VOLUME 62 • OCTOBER 1959 • NUMBER 4

OPHTHALMOLOGY

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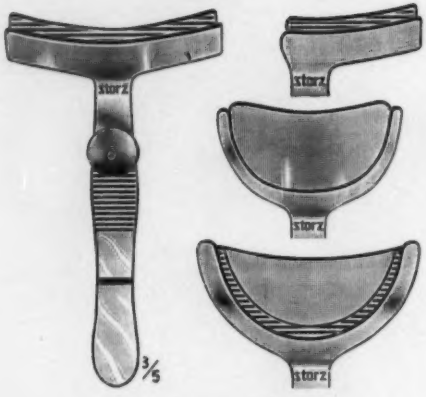

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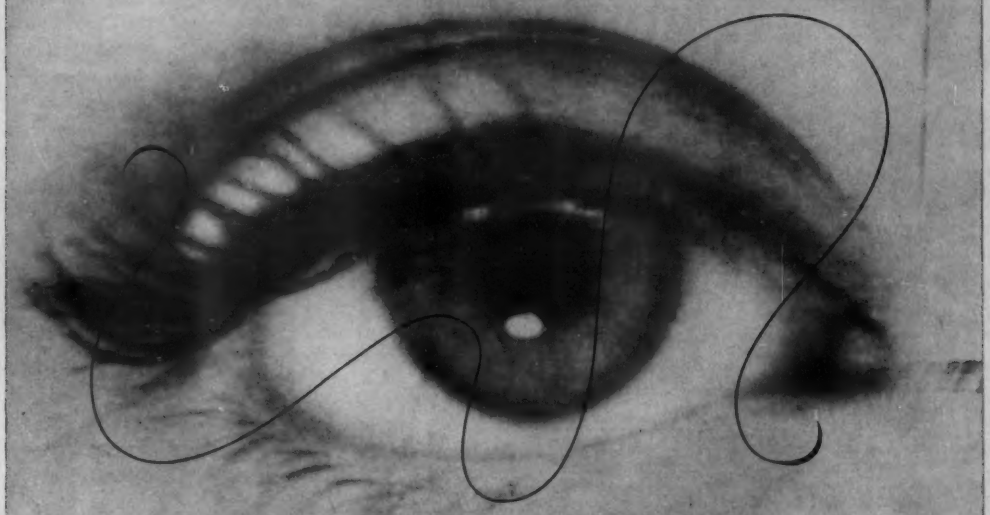

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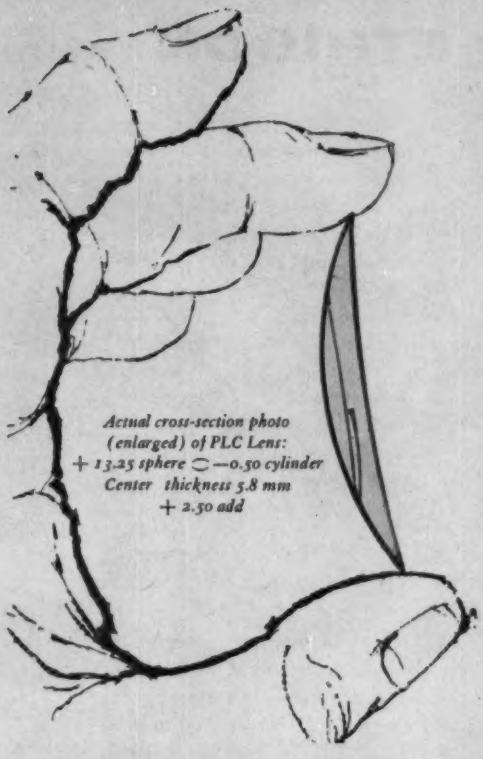

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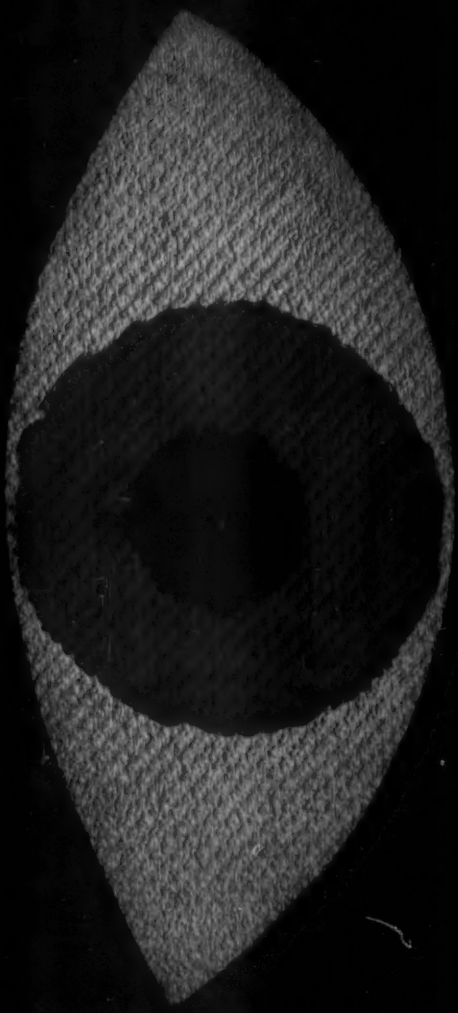

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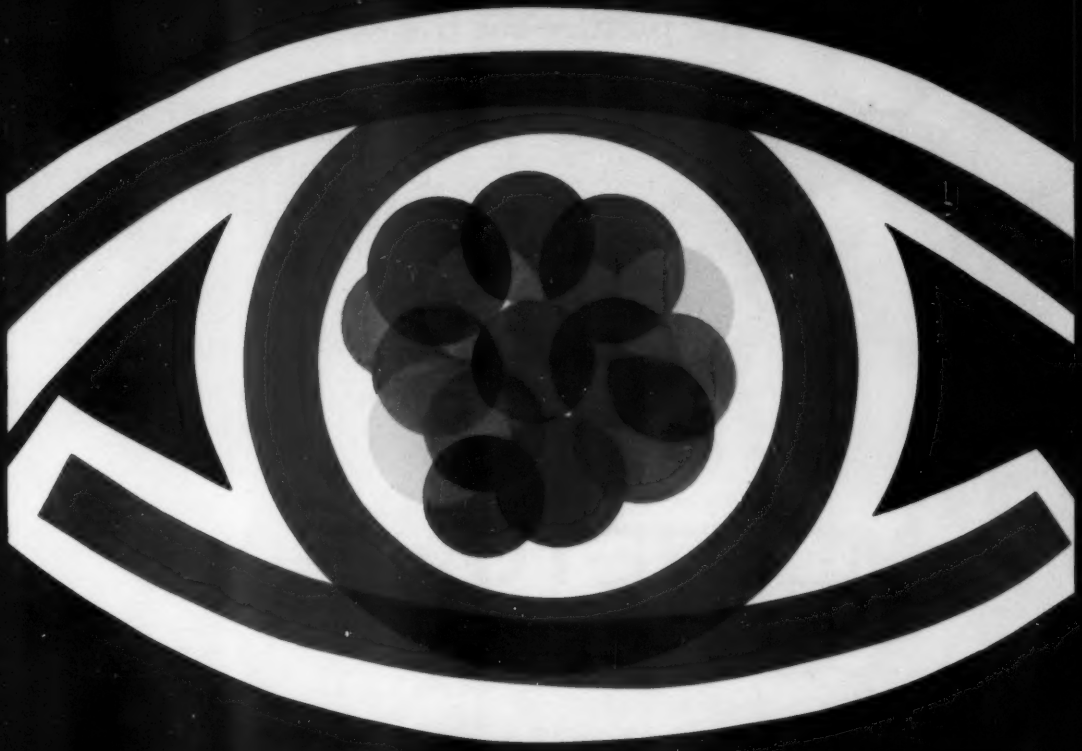

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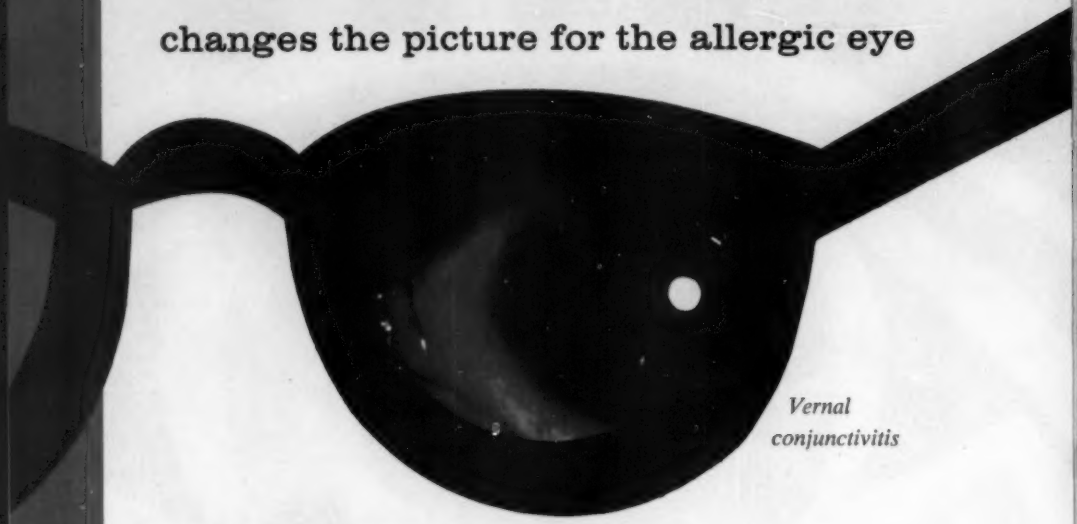

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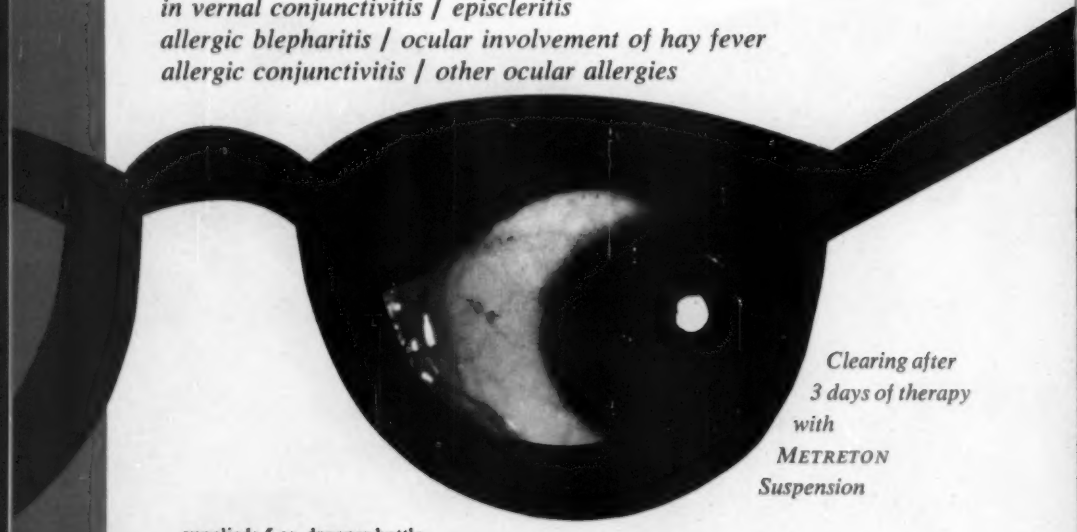

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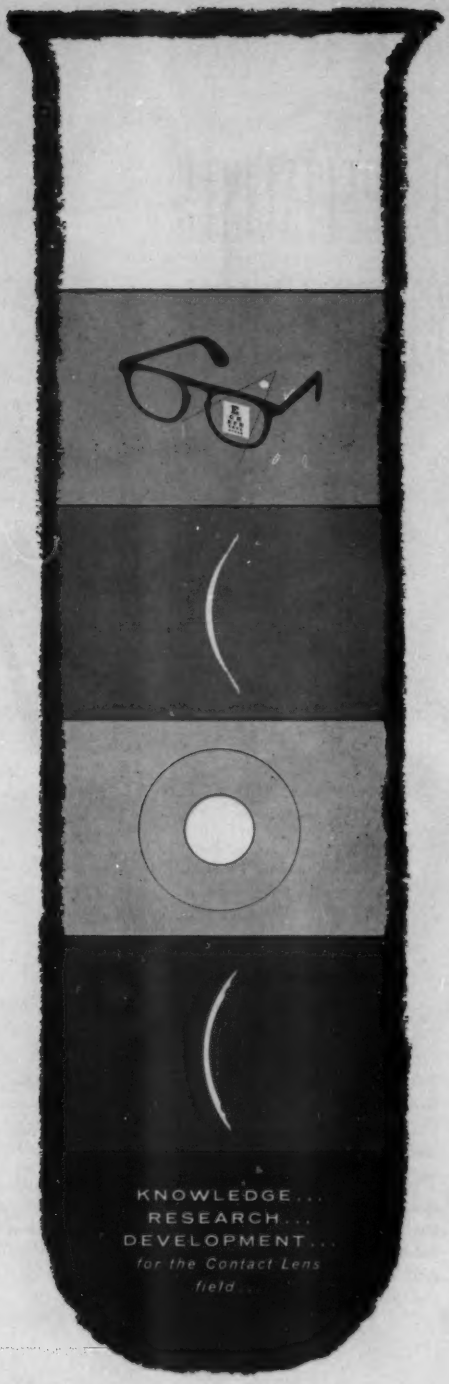

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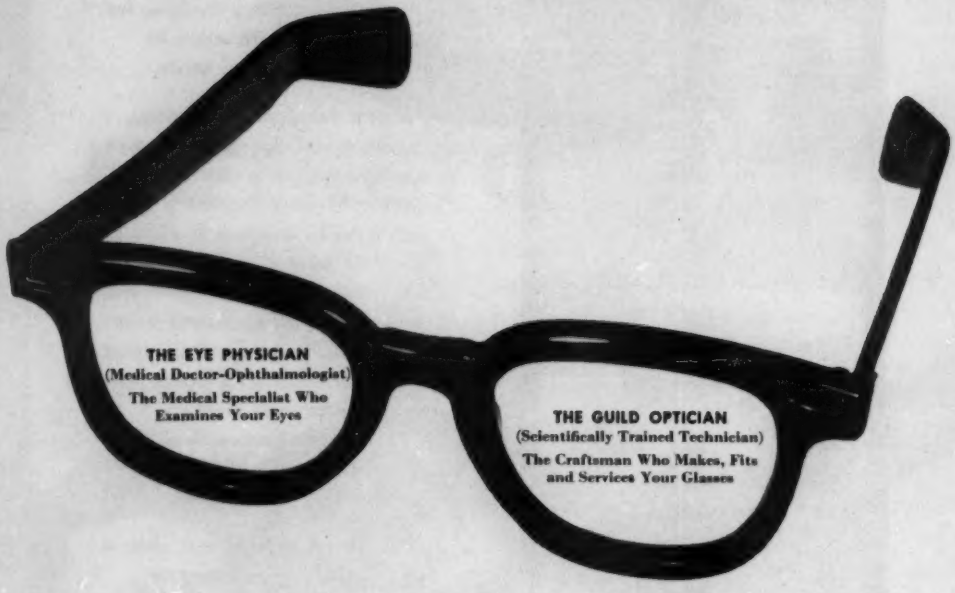
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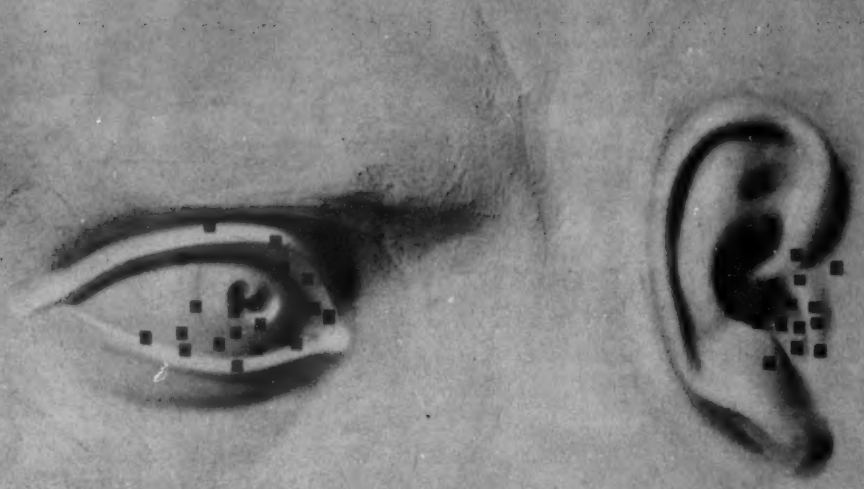

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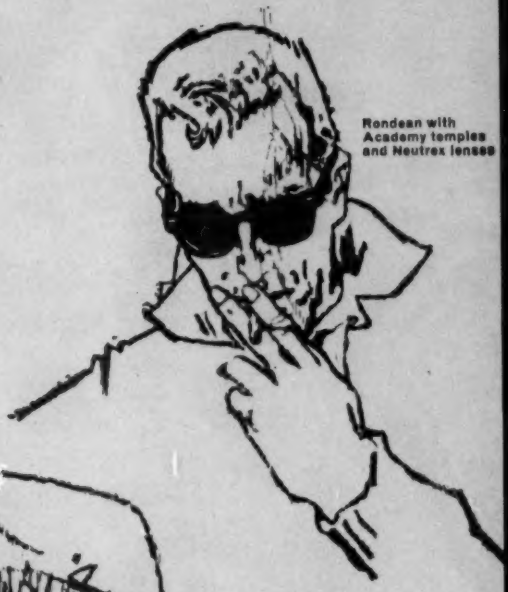

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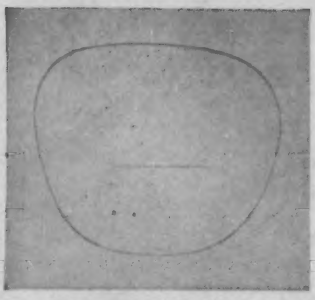

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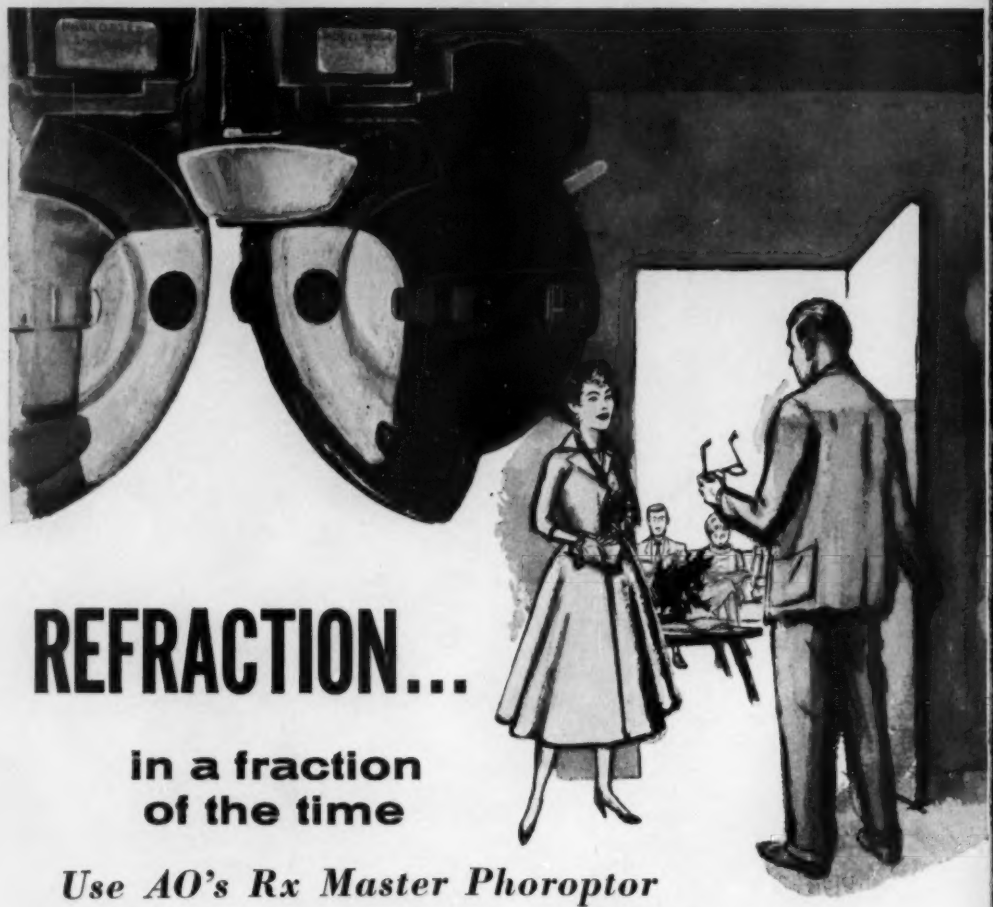

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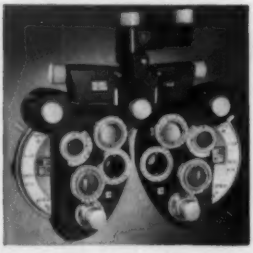

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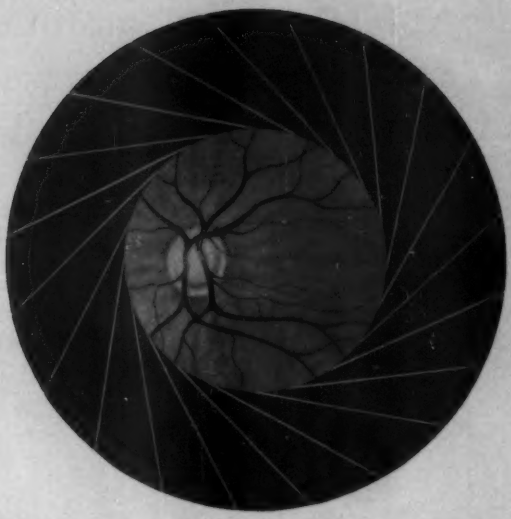

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1. Friedly, B. S., Medine, M. M. and Phillips, C. C. To be published. 2. Ahlquist, R. P. in Drill, V. A.: Pharmacology in Medicine, McGraw-Hill Book Company, Inc., New York, 1951, p. 18-28.

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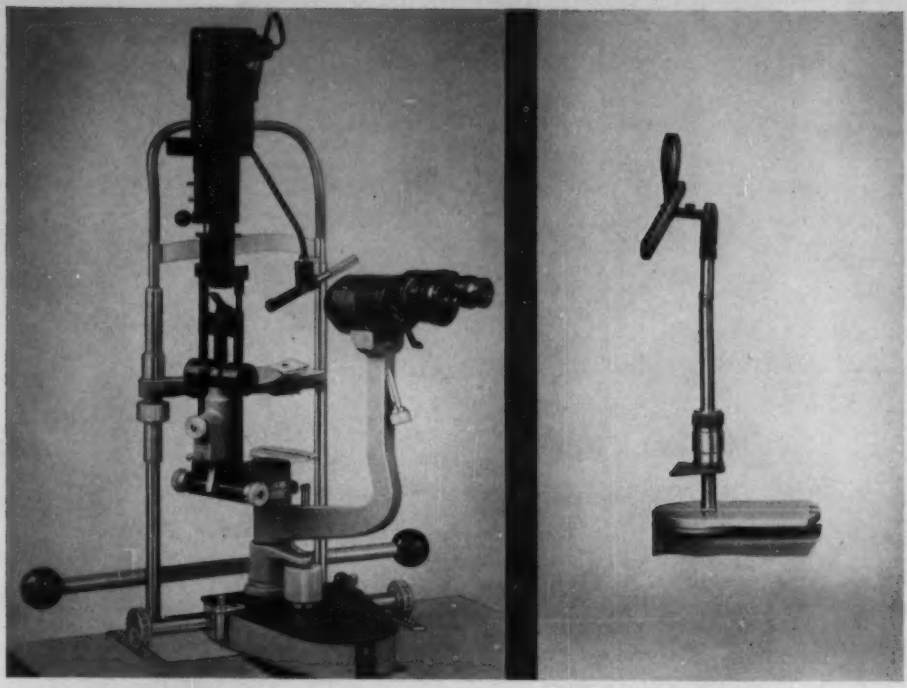

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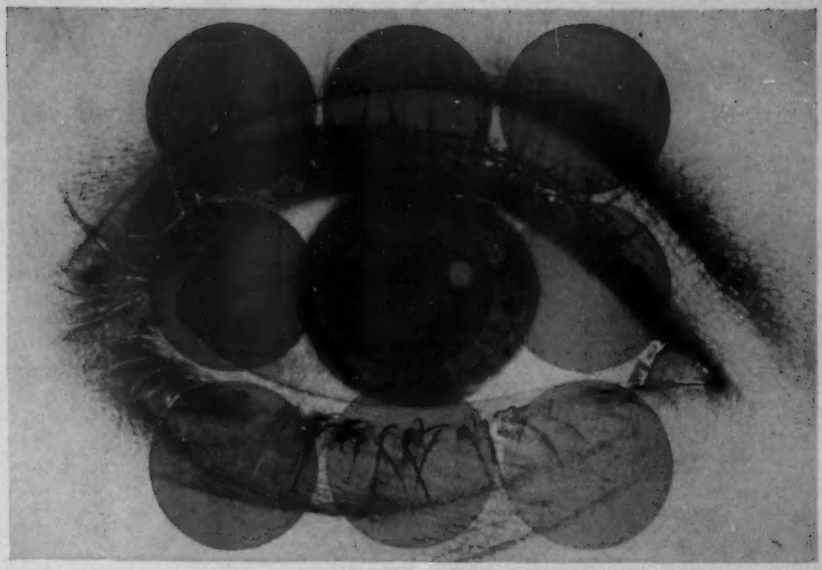

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1. New and Nonofficial Drugs; J. B. Lippincott Company, Philadelphia, 1958, p. 243.

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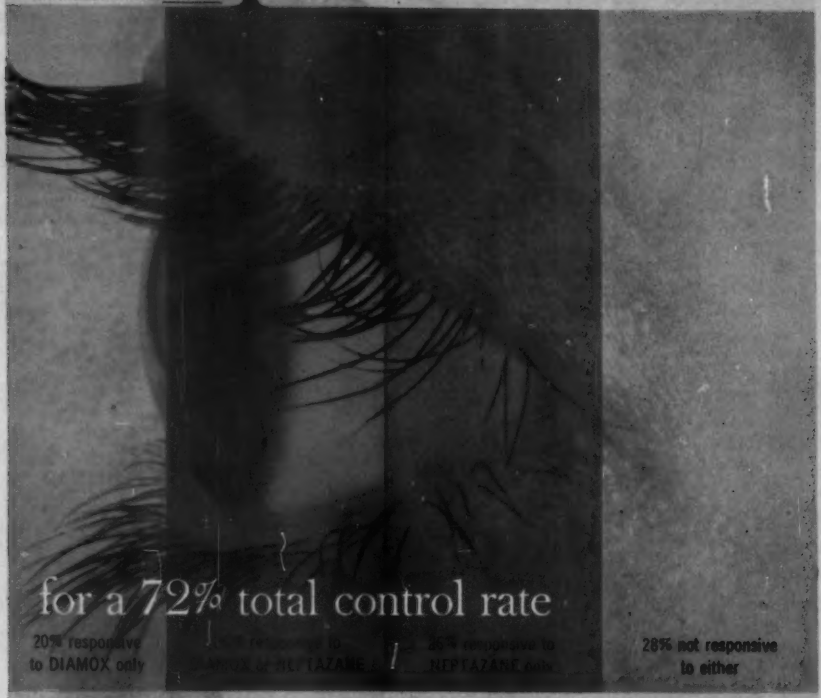

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Tumors of the Brain Stem with Special Reference to Ocular Manifestations

PAUL C. BUCY, M.D., and JAMES E. KEPLINGER, M.D., Chicago

The invitation received to address the Section on Ophthalmology is an honor indeed. This is doubly true under the chairmanship of your distinguished Dr. Frank B. Walsh, who has contributed so much in the field of neuro-ophthalmology.

The past 30 years have seen a great improvement in the diagnosis of tumors of the brain and particularly in their early recognition. Ophthalmologists especially have contributed to this progress. In the late 1920's and early 1930's between 75% and 85% of all patients with tumors of the brain had papilledema by the time they reached the neurological surgeon. Today not more than 30% of the patients who are operated upon for tumors of the brain have such ophthalmoscopic findings. This is obviously the result of the earlier recognition of these tumors and has enabled the neurosurgeon to improve his results and to lower the mortality from his operations. This earlier recognition has also increased the diagnostic problems. These have been met in some measure by the introduction of new diagnostic techniques, particularly pneumoencephalography and cerebral angiography. However, one cannot place complete reliance on any laboratory or mechanical diagnostic procedure. Almost daily we are confronted with patients harboring intracranial tumors in whom one or all of the diagnostic adjuvants are negative. It is important but not always easy to teach our young associates that a negative electroencephalogram, a normal x-ray film of the skull, or a normal pneumoencephalogram or a cerebral angiogram which demonstrates no abnormality does not rule out the possibility that the patient has a brain tumor. An alert, well-informed clinician is still the most important diagnostic instrument. A carefully taken history, an adequate and critically performed examination, and sound clinical judgment are his most important diagnostic tools.

Certain tumors of the brain are more likely to come first to the attention of certain medical specialists. Thus the patient with an acoustic neurinoma is usually first seen by the otologist, while one with a pituitary adenoma commonly first consults the ophthalmologist regarding his failing vision. Likewise, many of the patients with tumors of the brain stem first come to the attention of you men who concentrate on disorders of the eyes. This is true because so many of these patients develop disturbances of their ocular movements early in the course of their disease.

Received for publication June 25, 1959.

From the Northwestern University School of Medicine and the Section on Neurological Surgery of The Chicago Wesley Memorial Hospital.

Read before the Section on Ophthalmology at the 108th Annual Meeting of the American Medical Association, Atlantic City, N. J., June 12, 1959.

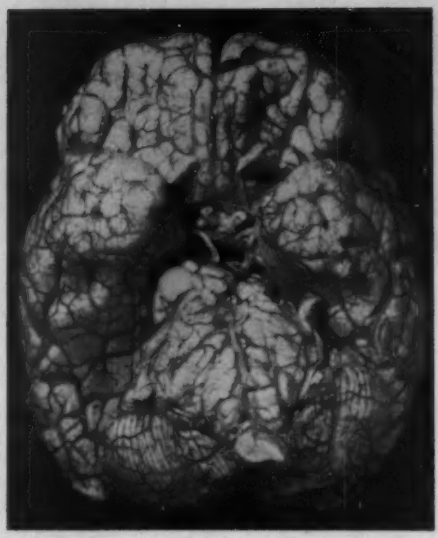

Fig. 1.—Typical glioma of the brain stem. The pons is greatly enlarged and nodular (Case 55 of Bailey, Buchanan, and Bucy).

Fig. 2.—Glioma of brain stem. The involvement is greatest in the pons, but the tumor extends forward into the mesencephalon and downward into the medulla oblongata (Case 53 of Bailey, Buchanan, and Bucy).

General Considerations

Before we proceed to discuss the ocular manifestations of tumors of the brain stem let us briefly review the general aspects of such tumors.

With rare exceptions intrinsic tumors of the brain stem are infiltrating gliomas. Microscopically they differ rather considerably, and we need not concern ourselves here with the differences of opinion regarding what terminology should be applied in classifying these tumors. It is important that we realize that these tumors develop in and occupy the pons predominantly (Figs. 1 and 2). As they are invasive they do not confine themselves to that portion of the neural axis but extend downward into the medulla oblongata and upward into the mesencephalon for variable distances (Fig. 2). Primary tumors of the medulla oblongata also occur but are rare (Fig. 8), while intrinsic gliomas involving the midbrain predominantly are somewhat commoner (Fig. 10 *a* and *b*). These tumors involve and destroy the nerve cells found in these areas, and thus manifestations of involvement of the various cranial nerve nuclei and of the vestibular nuclei are commonly seen with such tumors. The cells of the tumor tend to infiltrate among the nerve fiber pathways, often only pushing them aside without destroying their functions. Thus the evidences of involvement of the ascending sensory pathways, the descending motor tracts, and of the cerebellar connections vary widely from case to case. This tendency for these tumors to infiltrate among the fiber tracts in these cases was demonstrated clearly in a case which was reported by Bucy, Foerster, Gagel, and Mahoney. In that instance, although one side of the brain stem was extensively invaded by the tumor, and the tegmentum as well as the medullary pyramid and cerebellar peduncles appeared to be thoroughly invaded (Fig. 3), the patient had no signs of paralysis, no alteration in reflexes in the extremities, and no sensory disturbance. This case also demonstrated in a striking fashion that, although these tumors in general tend to involve both sides of the brain stem, they may be very asymmetrical. On the other hand, relatively symmetrical involvement of both sides of the pons is common (Fig. 4). In general, it may be said that the cerebellar pathways are least resistant to these tumors and the descending motor pathways are the next most susceptible, while clinical evidence of involvement of the sensory pathways is seldom found.

These tumors show no tendency to occur more often in one sex or, so far as is known, in any racial group (Bray, Carter,

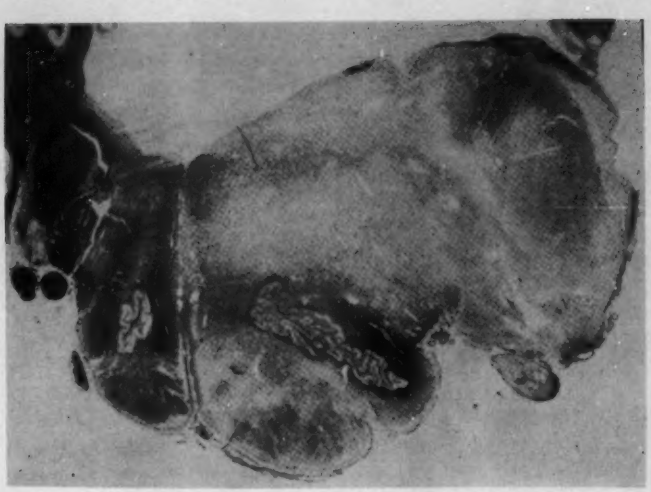

Fig. 3.—Glioma of the brain stem largely limited to one side. Although the medullary pyramid, the tegmentum, and the inferior cerebellar peduncle are extensively involved, there was no paralysis, alteration in reflexes, or change in sensory perception (after Bucy, Foerster, Gagel, and Mahoney).

and Taveras). There is, however, a great selectivity so far as the age of the victims is concerned. These are predominantly tumors of childhood. They only occasionally develop in patients over 20 years of age. In a random survey of 105 cases reported in the literature we found 63 in the first decade of life, 28 in the second, and only 14 in patients over 20 years of age (Fig. 5). The highest incidence was in children 5 to 9 years of age. In that age group 43.8% of the cases occurred. It is obvious that the diagnosis of an intrinsic tumor of the brain stem in an adult should always be suspect and should never be accepted without conclusive confirmatory evidence. The impor-

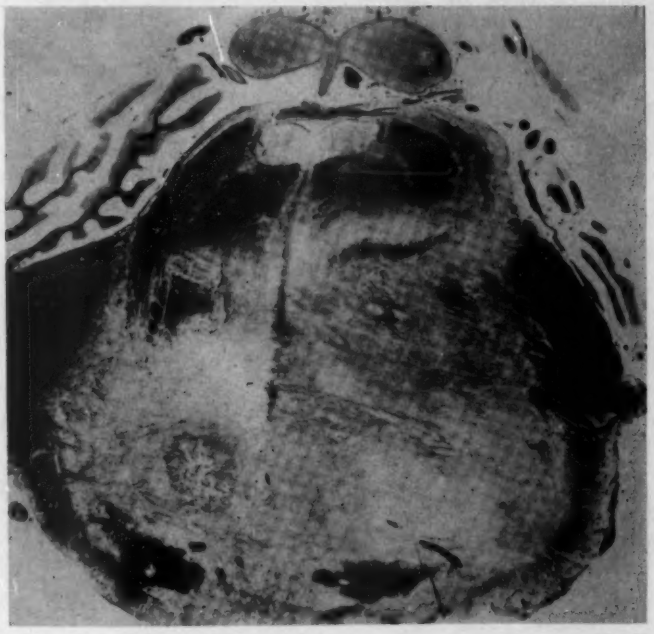

Fig. 4.—Glioma of the pons with more nearly symmetrical involvement (after Alpers and Yaskin).

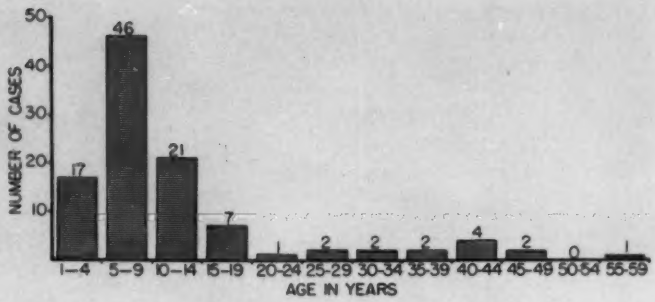

Fig. 5.—The age incidence of intrinsic tumors of the brain stem occurring in 105 cases selected from the literature. The predominance in patients less than 20 years of age is obvious. The peak incidence (43.5%) occurred in patients 5 to 9 years of age.

tance of this position will be substantiated later.

It may appear to some of my readers that we are speaking here of a very uncommon condition. Unfortunately such is not the case. Any neurological surgeon associated with a large pediatric service will attest to that fact. A number of years ago in their study of intracranial tumors in infancy and childhood, Bailey, Buchanan, and Bucy pointed out that intrinsic tumors of the brain stem form 15% to 20% of the intracranial tumors in patients under 15 years of age.

Signs and Symptoms

The onset of symptoms with intrinsic gliomas of the brain stem may be with the awkwardness and ataxia of cerebellar involvement, with the unsteadiness of gait which results from damage to the vestibular mechanism, or with the weakness of the extremities associated with lesions of the descending motor pathways. In many cases the initial symptom is the double vision and internal strabismus produced by involvement of the abducens nerve and the resulting paralysis of the lateral rectus muscle. In practically all cases some disturbance of the extrinsic or, less commonly, the intrinsic muscles of the eye develop sooner or later.

In the accompanying chart (Fig. 6) are recorded the incidence of involvement of the various cranial nerves in 100 verified cases of glioma of the brain stem taken from the literature and in 48 cases studied by Bray, Carter, and Taveras. The majority of the diagnoses in the cases studied by Bray, Carter, and Taveras were made by clinical means and had not been verified at the time of their report. Their cases were not as far advanced as those which we collected. This accounts for many of the differences in the two sets of figures. It will be noted in our figures that the *abducens (6th cranial) nerve* is the one most com-

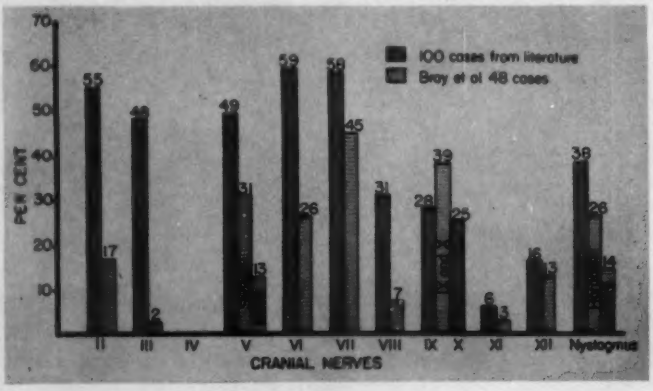

Fig. 6.—Involvement of various cranial nerves with gliomas of the brain stem. On the left (cross hatched) are the percentages from 100 verified cases taken from the literature (verification was usually by autopsy), and on the right (stippled) are figures from 48 cases studied by Bray and his associates. In their cases the diagnoses usually rested upon various clinical procedures, and the patients often were alive at the time of the study.

monly affected, and this has been the experience of most observers. Its importance is further advanced by the facts that it is often one of the first cranial nerves to be involved, its involvement is usually very obvious to the patient even when it is slight, and its involvement is commonly complete even early in the course of the disease. The involvement of the abducens nerve may be unilateral or bilateral. It is characteristic of tumors of this type that such a paralysis of the lateral rectus muscle is rather frequently associated with a paralysis of *lateral conjugate deviation* of the eyes to the side of involvement or with an abolition of all movement of both eyes in a horizontal plane in cases where both abducens nuclei are involved. It appears likely that this paralysis of lateral conjugate deviation is due to interference with the connections between the abducens nucleus and the oculomotor (3d cranial nerve) nucleus, which innervates the contralateral internal rectus muscle which is responsible for the lateral deviation of the eye opposite the paralyzed abducens nerve. The connection between the abducens and the oculomotor nuclei takes place through the median longitudinal fasciculus (Fig. 7).

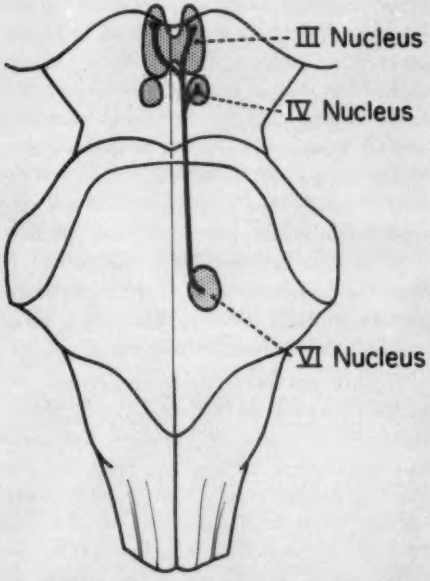

Fig. 7.—Connections through the median longitudinal fasciculus between the nuclei of the various cranial nerves (3d, 4th, and 6th) which innervate the ocular muscles.

This involvement of lateral rotation of the eyes is probably the most characteristic finding in cases of pontine tumors. It is not that external rectus palsies do not occur in other conditions, for they do, but *the development of an abducens paralysis in a child in the absence of increased intracranial pressure, particularly if it is associated with a paralysis of lateral conjugate movement of the eyes or with the involvement of other cranial nerves, is highly suggestive of the possibility of a pontine glioma.* A number of years ago Bucy and Weaver pointed out that a paralysis of conjugate deviation of the eyes occurred not infrequently with cerebellar abscesses but that such lesions are usually associated with severely increased intracranial pressure at the time of such a development whereas gliomas of the pons are not. Furthermore, fortunately, in this era of antibiotics cerebellar abscesses have become relatively uncommon. It is surprising that cerebellar tumors, unlike abscesses, are rarely associated with a paralysis of conjugate deviation of the eyes, although such a development has been reported (Brain). These cerebellar lesions undoubtedly produce their effects by compression of the brain stem rather than as a result of a disturbance of cerebellar function. A paralysis of lateral conjugate movement of the eyes may be seen with vascular disorders of the brain stem. Such disorders usually are the result of occlusive or hypertensive vascular diseases and therefore are most common in adults. When vascular disturbances develop in the brain stem of children they are usually due to vascular anomalies, and these are rare (see below).

Persistent disturbances of conjugate lateral movement of the eyes are almost always the result of involvement of the pons, but *transitory* disturbances of conjugate lateral movement, both of an irritative and a

paralytic character, may be seen with lesions of the frontal lobes of the cerebrum. Such transitory disturbances of conjugate lateral movement of the eyes are seen only with acute disorders in the frontal lobes, never with chronic ones. Their sudden onset and brief duration as well as the absence of other symptoms indicative of pontine involvement readily serve to differentiate the frontal lesions from those in the pons.

In view of the close relationship within the pons of the fibers of the *facial nerve* to the abducens nucleus, it is not surprising to note that in these 100 cases a facial paralysis was practically as common as a paralysis of the external rotation of the eye. Bray, Carter, and Taveras found facial paralysis to be considerably commoner than 6th nerve paralysis in their 48 cases, but such has not been the experience of other observers.

Another wide discrepancy between the figures of Bray, Carter, and Taveras and our own concerns the manifestations of involvement of the *oculomotor, or 3d cranial nerve.* We found such involvement reported in 48 of 100 cases, whereas they reported it in only 2% of their 48 cases. It seems likely that the difference in these two sets of figures lies in the fact that the 100 cases we collected from the literature were more advanced and of longer duration than were the cases reported by Bray and his associates. Evidence of implication of the 3d cranial nerve often comes late in the course of the illness as the tumor which has originated in the pons extends upward to involve the midbrain. Furthermore, one seldom sees a complete paralysis of the 3d nerve. Usually there is a unilateral or bilateral partial ptosis, a dilatation and inequality of the pupils with an impairment of the reaction to light on one or both sides. This is in contrast with the involvement of the innervation of the lateral rectus muscle, where a complete paralysis is commonly found. Extension of the tumor upward into the midbrain may also result in an impairment of *upward rotation of the eyes.* This syndrome (Parinaud's) is typical of any involvement of the mesencephalic tectum and is generally regarded as particularly characteristic of tumors of the pineal body. In any event, it must be borne in mind that gliomas of the brain stem may also give rise to this condition.

It will come as no surprise to ophthalmologists that evidence of damage to the *trochlear, or 4th cranial, nerve* is seldom found. Under any circumstances paralysis of the superior oblique muscle is difficult to establish, and in cases in which paralyses of other external ocular muscles exist its demonstration is almost impossible.

Nystagmus is a common finding with gliomas of the pons. Our survey disclosed its presence in 38% of the cases, while Bray, Carter, and Taveras found a horizontal nystagmus in 26% and a vertical one in 14% of their 48 cases. There is nothing particularly characteristic or diagnostic about this nystagmus. It seems most likely that it develops secondarily to damage to the vestibular nuclei.

The *5th cranial, or trigeminal, nerve* is involved almost as commonly as the 6th and 7th. According to Bray, Carter, and Taveras, the sensory division is implicated more than twice as often as the motor. Such involvement not only gives rise to a loss of facial sensibility but to an anesthesia of the eye as well. This latter abolishes the corneal reflex and renders the cornea susceptible to injury and ulceration, particularly if it is impossible for the patient to close the eyelids because of a facial paralysis. As we have noted earlier such a facial paralysis is common in these cases.

We are not particularly concerned here with involvement of the other cranial nerves. However, a glance at Figure 6 will show that impairment of hearing, from involvement of the *8th cranial nerve,* and of swallowing, from implication of the *9th and 10th,* are by no means uncommon. That the *11th cranial nerve,* which is largely of spinal origin, and the *hypoglossal,* which lies most caudad in the brain stem, are

involved less often than the other cranial nerves is to be expected.

It has become routine to say that unlike other intracranial tumors gliomas of the pons are seldom associated with *increased intracranial pressure*. This statement may be misleading. In the first place, with the general improvement in their early recognition few brain tumors are associated with marked evidence of increased intracranial pressure, such as *papilledema*, when they are diagnosed today. Second, a glance at Figure 6 will reveal that papilledema is by no means a rarity with intrinsic tumors of the brain stem. However, we must not overlook the fact that the figures given there were for the most part accumulated many years ago. In any event, the development of papilledema with intrinsic tumors of the pons generally occurs late in their course. It is for this reason that papilledema was found more frequently (55%) in the 100 verified tumors than in the series of Bray, Carter, and Taveras, where it occurred in only 17% of these less advanced cases. At the time when the patient is likely to be brought to the ophthalmologist because of double vision or a squint, it is unlikely that he will have papilledema, that the sutures of the skull will be found to be separated in an x-ray examination of the head, or that the pressure of the spinal fluid will be elevated above a normal level. In the early stages the cerebral ventricles will show little or no dilatation, although at autopsy some enlargement of the ventricles is likely to be present.

In spite of the fact that signs of increased intracranial pressure tend to develop late if at all with tumors of this type, *headache* commonly appears early but is seldom as severe as with the other tumors of the brain which arise in childhood.

In addition to the symptoms of involvement of the various cranial nerves, tumors of the pons are frequently associated either at the onset or later with *nausea*, *vomiting*, and *dizziness*. The vomiting, the lack of appetite, and the difficulty in swallowing due to paralysis of the soft palate and pharynx (9th and 10th cranial nerves) result in a marked loss of weight. The *emaciated* condition of many of these children is characteristic of the disease and is in striking contrast to the obesity commonly seen in children with tumors in and near the 3d ventricle.

We have noted earlier that descending motor pathways and cerebellar connections are commonly disrupted with tumors of this type. Such involvement results in *paralyses of arms and legs*, in *awkwardness* of the movements which are present, and of severe *disturbances of gait and equilibration*.

It should be noted again that, although many nerve fibers and nerve cells may survive and continue to function for a long time within one of these tumors, one group of fibers are particularly resistant. All observers are agreed that alterations in *sensory perception* of any type in the trunk and extremities are rarely seen as the result of a glioma of the pons. An exception must be made for the sensory changes which commonly develop in the face. These are the result of the involvement of the nuclei of the trigeminal nerve.

Thus far our attention has been concentrated upon tumors of the pons, but occasionally we see tumors which involve the *medulla oblongata* predominantly. In Figure 8 such a tumor is shown. Its clinical manifestations, which were not particularly characteristic, were as follows:

CASE 1.*—This boy developed a temporary difficulty in swallowing at the age of 3 years. A month or so later pain and stiffness of his neck appeared. These grew worse, and he took to his bed and resisted all attempts to move his head. On examination, his optic fundi were normal and there were no detectable abnormalities of his cranial nerves. His tendon reflexes were hyperactive, and Babinski's sign was present bilaterally. Examination of his spinal fluid gave no assistance in arriving at a diagno-

* This case was previously reported by Bailey, Buchanan, and Bucy as Case 51.

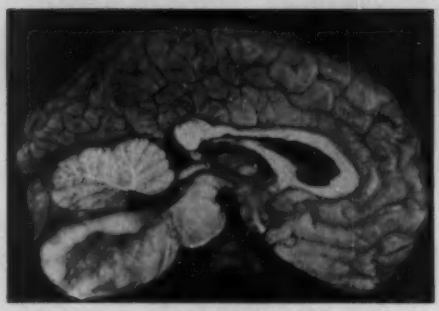

Fig. 8.—Glioma of the medulla oblongata (Case 51 of Bailey, Buchanan, and Bucy).

sis. His condition improved. Three weeks later he became irritable, and again his neck became rigid. Nystagmus was produced when he looked to the right or left; his left hand became awkward and his standing and walking unsteady. Again he improved. Six months later he returned with weakness of both external rectus muscles, nystagmus on looking to right or left, gross incoordination of all four extremities, generally increased tendon reflexes, and bilateral signs of Babinski. He was unable to stand or walk alone. A diagnosis of a tumor of the posterior fossa was made. He was operated upon. The tumor (Fig. 8), of course, could not be removed.

Comment.—There is nothing particularly diagnostic about the course of this illness or the findings on examination, and it serves only to emphasize how difficult diagnosis in these cases may be and how many nerve cells and fibers may exist and continue to function within the substance of the tumor.

Gliomas within the midbrain are somewhat commoner. They often give rise to one of two syndromes: Benedikt's and Weber's. Benedikt's syndrome is due to the involvement of the mesencephalic tegmentum, particularly of the fibers of the 3d cranial (oculomotor) nerve where they pass through the red nucleus and to destruction of the fibers of the cerebellorubrothalamic tract. Such involvement results in an ipsilateral 3d nerve palsy (ptosis, dilated fixed pupil, and a paralysis of the superior, internal, and inferior recti and of the inferior oblique muscles) and an ataxia with intention tremor of the contralateral arm and leg. Weber's syndrome, which is the result of involvement of the base of the midbrain, is well illustrated by the following case:

Case 2.†—This patient was referred by Dr. Lawrence Russell, of Cicero, Ill. This girl was well until the age of 4 years, when her right upper eyelid began to droop. A month later a weakness of the left side of the face appeared, and her left arm and leg grew progressively more paralyzed. Two months after the onset of symptoms she first complained of headache and vomited. On examination she was restless and stuporous. She had a ptosis of the right upper eyelid. The right pupil was dilated and did not react to light. The right eye was rotated outward and downward. The left arm and leg were paralyzed and spastic (Fig. 9). All tendon reflexes were hyperactive, and Babinski's sign was present in both feet. There were no detectable alterations in sensation. A diagnosis of a tumor of the right side of the midbrain was made, and x-ray therapy was begun. Her condition rapidly failed, and she died after three treatments (430 r) had been given. Autopsy disclosed the expected tumor. It was an oligodendroglioma which involved the right cerebral peduncle and right side of the midbrain predominantly. It extended forward into

† This case was previously reported by Bailey, Buchanan, and Bucy as Case 64.

Fig. 9.—Child with glioma of midbrain. She has a ptosis on the right side and a hemiplegia on the left, with the left arm drawn up in flexion and the left leg rigidly extended.

Fig. 10.—Oligodendroglioma of the midbrain. (*a*) View of the base of the brain showing the nodular tumor lying just anterior to the pons. The tumor lies predominantly to the right of the midline of the brain (to the left in the photograph). The third cranial nerves are seen protruding from its surface. (*b*) Cross section through the midbrain and tumor showing the third cranial nerves protruding downward.

the posterior hypothalamus and upward and laterally into the right internal capsule and basal ganglia. It also involved the upper part of the pons (Fig. 10).

Here the diagnosis was easy and the symptoms exactly what were to be expected from a tumor in this location.

Occasionally tumors other than gliomas are found within the brain stem. Dandy refers briefly to a hematoma which he successfully evacuated from the pons. He very reasonably suspected that this hematoma might have arisen from an angioma within the pons. Percival Bailey had a similar case in which postmortem examination demonstrated the presence of a hemangioma in association with a hemorrhagic cyst within the pons (Fig. 11).

CASE 3.—Bailey's patient was an 8-year-old girl who gave a history of recurring episodes of headache, nausea, and vomiting for four months. She had a progressively increasing dysarthria, left hemiparesis, and drooping of both upper eyelids. Eventually she developed a bilateral paralysis of the muscles of mastication and of the soft palate and pharynx, a moderate ataxia of the right arm and leg, and bilateral Babinski's sign. She became lethargic, then stuporous, and she died.

Examination of the brain disclosed a large hematoma occupying most of the pons (Fig. 11 *a*). This finding was very reminiscent of Dandy's case. Microscopic examination of the walls of the hemorrhagic cavity disclosed the presence of a telangiectasis which had given rise to the hemorrhage (Fig. 11 *b*).

Such cases are so rare that no typical clinical picture can be developed. It is to be expected that, as in Dandy's case, these patients would have remissions and long quiescent periods and that in some instances evidence of subarachnoid bleeding might appear. We have seen other cases in which this diagnosis has been suspected but not verified.

The brain stem may also be involved by various extrinsic tumors. Meningiomas and acoustic neurinomas are the commoner of these.

Acoustic neurinomas are usually readily recognized, as they generally begin with unilateral deafness and tinnitus. They often do not produce much in the way of ocular manifestations, except for a loss of the corneal reflex. Diplopia may at times occur but is seldom associated with more than a very mild weakness of the external rectus

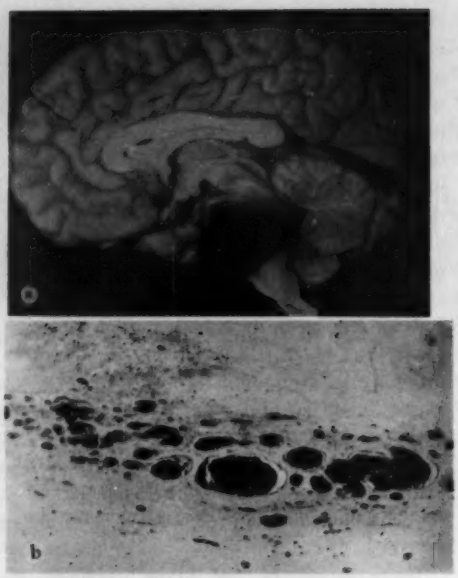

Fig. 11.—Hematoma of pons arising from a hemangioma. (*a*) Sagittal section of brain showing the hematoma occupying most of the pons. (*b*) Photomicrograph of the wall of the cavity demonstrating the hemangioma (courtesy of Dr. Percival Bailey).

muscle. Papilledema, which formerly was present in most such cases, now is seen much less commonly, as the diagnosis is being made earlier in the course of the disease. Meningiomas of the cerebellopontine angle generally present a very similar picture, but some meningiomas in other parts of the posterior fossa present a puzzling clinical picture suggestive of a tumor of the brain stem itself. The following case illustrates this point:

Case 4.‡—This patient was referred by Dr. J. M. Krupka, of Cicero, Ill. This 44-year-old woman first developed numbness of her tongue and soon of the entire mouth about four years before her admission to the hospital on May 10, 1949. A year later twitching of the right side of her face and unsteadiness of her walking appeared. Her condition then remained stationary for two years. A year before admission she developed weakness of her right arm and leg, slurring of her speech, regurgitation of fluid through her nose, suboccipital headaches, and attacks of severe pains in the *left* side of her face. Examination revealed no papilledema. There was a convergent strabismus and a weakness of conjugate lateral deviation of the eyes to both right and left. There was a coarse nystagmus on attempting to look to either side. Both corneal reflexes were absent. She had a hypalgesia of the face bilaterally. The muscles of mastication were weak on the left side. There was a facial weakness and partial deafness on the right. The 9th and 10th nerves were involved bilaterally. The spinal accessory and the hypoglossal nerves were partially paralyzed on the right. She had evidence of cerebellar dysfunction in the right extremities. Pain and temperature sensibilities were decreased on the right half of the body. All tendon reflexes were hyperactive, and Babinski's sign was present on the right side. The pressure of the spinal fluid was not increased. She died suddenly a short time after admission, and, to our surprise, an autopsy did not disclose the glioma of the brain stem which we expected but a large meningioma in the left side of the posterior fossa which severely compressed the brain stem (Fig. 12).

Fig. 12.—Meningioma occupying the left side of the posterior fossa (on the right in this photograph) compressing the cerebellum and brain stem (after Russell and Bucy).

‡ This case was previously reported by Russell and Bucy as Case 2.

Comment.—This case serves to illustrate two very important related points. Meningiomas in the posterior fossa may cause multiple cranial nerve palsies and evidence of involvement of the nerve fiber pathways in the brain stem without producing any evidence of increased intracranial pressure. They may closely simulate the picture produced by a glioma of the brain stem, except that they almost always occur in adults. As intrinsic tumors of the brain stem usually occur in children, approximately 87% in patients under 20 years of age, a diagnosis of a glioma of the brain stem should not be made in people over 20 years of age without adequate proof of correctness. In the majority of adults where a glioma of the brain stem is suspected, the posterior fossa should be explored surgically.

There are other lesions which may be confused with gliomas of the brain stem, but all are relatively rare in North America. In some parts of South America, particularly in Peru, *cysticercosis* commonly develops in the cerebellopontine angle and affects one or more cranial nerves. Increased intracranial pressure is usually present early. *Chordomas* arising from the base of the skull just posterior to the sella turcica are a rare condition which may also compress the brain stem. Multiple sclerosis, vascular disorders of the brain stem, and inflammatory lesions seldom cause confusion in children but occasionally may pose interesting differential problems in adults. The following cases illustrate the problems in diagnosis.

CASE 5.—This woman was referred by Dr. S. V. Haraburda, of Chicago. She was born in 1921. On Jan. 14, 1951, she began to complain of blurred vision and diplopia. Her family stated that she had always been rather slow mentally and her speech had always been slurred.

Examination on Feb. 6, 1951, revealed a dull, apathetic, childish woman with a slurred speech. Her optic fundi were normal and her visual fields full. There were no horizontal movements of either eye, except that she could converge on near objects. Vertical ocular movements were normal. The pupils were not unusual. Her hearing was markedly reduced on the right, but there were changes in the right tympanic membrane. The other cranial nerves were normal. There were no sensory changes. Muscular strength, tone, and coordination were good, but her gait was a little unsteady. The reflexes were not abnormal. By Feb. 12, the movements of the internal recti had recovered but the lateral recti were still paralyzed. The spinal fluid was normal except for the presence of 14 lymphocytes per cubic millimeter.

She recovered from this condition and remained well until March 1, 1959 (eight years later), when she developed diplopia on looking to the right. Examination on March 9 revealed only a slight weakness of the right lateral rectus muscle. This condition also improved, and by May 11 she had practically recovered.

Comment.—Initially the diagnosis seemed to lie between an encephalitis of the brain stem and multiple sclerosis. Because of the absence of evidence of involvement of other cranial nerves or of the nerve fiber pathways in the brain stem the possibility of a glioma of the brain stem was not seriously considered. Although such striking paralyses of the extraocular muscles are not usual in multiple sclerosis, the recovery and the recurrence of symptoms eight years later make multiple sclerosis the most likely diagnosis in this case.

The following case also presented serious difficulties in differential diagnosis:

CASE 6.—This woman was referred by Dr. G. Gertz, of Chicago. She was 39 years old when she developed severe constant headache and vomiting, beginning late in November, 1952. At the same time she suddenly developed a paralysis of the right arm and leg. There were also involuntary kicking movements of the right leg. The right side of her face became weak. She had great trouble talking and complained of vertigo.

On general physical examination the only abnormality was a blood pressure of 170/106. Neurological examination on Nov. 24, 1952, disclosed a lethargic but cooperative woman. Her speech was so dysarthric that it was difficult to understand her. The optic discs and retinae were normal. The pupils were normal and ocular movements were full, but there was some nystagmus with the eyes at rest and marked nystagmus on looking in any direction. There was a slight right lower facial weakness. The pharynx was filled with mucus, and she had great difficulty in swallowing. The protruded tongue deviated to the left. The other cranial nerves seemed intact. The right hand and fingers were very tender, and manipulation or movement of them was very painful. There was a severe paresis of the right extremities, more marked distally. Resistance to passive manipulation was decreased in the right extremities, and the tendon reflexes were not very different on the two sides. Babinski's sign was present on the right. All abdominal reflexes were very sluggish. It was impossible to test her station or gait because of her weakened condition.

X-ray examination of the skull and chest revealed no abnormality. The urine was concentrated and contained a moderate amount of acetone. The blood count and the Wassermann and Kahn tests were normal.

On lumbar puncture the initial pressure was 170 mm. of fluid. The fluid contained 12 red blood cells, 2 lymphocytes, and 8 polymorphonuclear leukocytes per cubic millimeter. The total protein was 36 mg. per 100 cc. of fluid. The colloidal gold curve was 0000000000.

With general supportive measures her general condition rapidly improved, but she developed an almost complete anesthesia of the right side of the forehead, with a less severe sensory loss over the right cheek and chin. She became able to swallow water well, but the right side of the soft palate and the left side of the tongue were still paralyzed. The nystagmus was still present. There was an astereognosis in the right hand, but the hypersensitivity disappeared. The right hemiparesis became almost complete. The tendon reflexes became a little more active on the right, and Babinski's sign was still elicitable on the right.

By Dec. 1 stereognostic sensibility was returning to the right hand, but two days later examination disclosed a reduction in the perecption of pain over the left side of the chest and slight ataxia with the left extremities; the right ones were still paralyzed. On Dec. 12 she was able to walk poorly with help. Thereafter her ability to walk steadily improved, although her gait has continued to be unsteady. She has been examined frequently since, the last time on June 3, 1959. Her speech and swallowing were normal. Nystagmus was present on looking in any direction. Her hearing was reduced slightly on the right. There was a left hemiatrophy of the tongue with fasciculation. The tongue deviated slightly to the left on protrusion. There was a slight right lower facial weakness and a very slight weakness of the right extremities. Tone was slightly increased in the right lower extremity. All tendon reflexes were increased in the right extremities, and Babinski's sign was present on the right. There was a hypalgesia in the right forearm; otherwise, sensation was normal everywhere. She favored the right lower extremity as she walked. She does her own housework and is only slightly incapacitated. Her condition seems stationary.

Comment.—Again one can only say with certainty that the brain stem has been seriously involved. In this case the acute onset and the recovery with certain fairly stationary residuals makes it seem likely that this woman suffered from an encephalitis of the brain stem. Such infections rarely if ever develop in children.

Aneurysms are uncommon in the posterior fossa, although by no means unknown. In the following case it seems likely that an aneurysm was present and gave rise to

evidence of involvement of several cranial nerves.

CASE 7.—This patient was referred by Dr. Henry Christiansen, of Chicago. The patient was a young man, 27 years old when he was first seen as an outpatient on July 25, 1945. He stated that he had suffered from pain and tightness in the right side of his face for three years and a paralysis of lateral rotation of his right eye for two years. Examination disclosed a complete paralysis of the right lateral rectus muscle and a slight weakness of the right side of the face and the right side of the soft palate. The spinal fluid and roentgenograms of his skull and chest were all normal.

On May 6, 1946, examination disclosed the paralysis of the external rectus muscle and a sluggish reaction of the right pupil to light, an absent right corneal reflex, and hypesthesia of the right side of the face to pin and cotton. The spinal fluid was still normal. Further investigation was advised but was refused.

On May 3, 1947, he developed a spontaneous subarachnoid hemorrhage which was confirmed by spinal puncture. On May 5, he suddenly cried out with pain in the right side of his face and died in a very few minutes. An autopsy was not obtained.

Comment.—Almost certainly this man suffered from some vascular anomaly. It may have been an aneurysm or some other vascular malformation. In the absence of definitive diagnostic tests or an autopsy, a more specific diagnosis is not possible.

These latter are all diseases with involvement of several cranial nerves and with or without involvement of the long fiber tracts in the brain stem. They only superficially imitate the clinical picture produced by a tumor of the brain stem. It is noteworthy that all of these latter patients were adults and that the symptoms began rather suddenly. Furthermore, the picture lacks that steady progression so commonly seen with gliomas of the brain stem.

Summary

Intrinsic tumors of the brain stem are usually gliomas of various types. They most commonly involve the pons but may extend upward or downward from there. Ocular disorders, particularly paralysis of the external rectus muscles and of conjugate lateral movements of the eyes, are among the commonest manifestations. Involvement of the 3d cranial (oculomotor) nerve usually appears late, if at all, and is usually incomplete, producing only pupillary disturbances and a partial ptosis. An exception are those less common cases in which the tumor arises in the midbrain rather than in the pons. Other cranial nerves, particularly the facial (7th), trigeminal (5th), auditory-vestibular (8th), glossopharyngeal (9th), and vagus (10th) are commonly involved. Increased intracranial pressure with papilledema is not uncommon but usually develops late in the course of the disease. The descending motor pathways and cerebellar connections are almost always affected, but sensory changes in the trunk and extremities are almost never found.

Headache, nausea, and vomiting are common complaints. The anorexia plus the common difficulty in swallowing frequently produces an emaciation of the patient.

Gliomas of the brain stem usually are disorders found in patients under 20 years of age. Symptoms suggestive of such a tumor in an adult should be investigated most carefully. They may be due to a benign removable tumor, such as a meningioma, or to some other less common disorder. There are numerous conditions which may occasionally involve the brain stem and have to be considered in differential diagnosis.

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Activity of the Oculorotary Muscles During Tonometry and Tonography

An Electromyographic Study

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It is well known that holding a tonometer near the eye or putting it on the cornea causes the patient to squeeze his lids because of a contraction of the orbicularis muscles. This reflex occurs regularly at the sight of an object near the eye and is generally termed a protective or fright reaction. Little attention has been paid to the part played by the oculorotary muscles during the so-called fright reaction.[1,2]

This study was undertaken to elucidate the reaction of the oculorotary muscles to tonometry and tonography. This seemed important in view of the pronounced influence the oculorotary muscles exercise on the intraocular pressure.[3] Changes in the state of contraction of the oculorotary muscles might alter the ocular tension and introduce some inaccuracies in tonometric and tonographic measurements.

Materials and Methods

The measurements of ocular tension and of electrical activity of the oculorotary and orbicularis muscles were performed on 19 patients between the ages of 10-70 years. There were 9 males and 10 females. The visual acuity ranged from no light perception to 20/20. The patient lay on an examining table in an electrically shielded cage made of copper window screening. The electromyographic technique used here and the interpretation of the electromyograms is described in detail elsewhere.[4,5] In all the cases electrodes were inserted into at least two of the recti of one eye; in the majority of patients an agonist and the antagonist were recorded simultaneously. In a number of patients the activity of the horizontal recti of both eyes were measured at the same time, and in one case all four recti muscles of one eye were recorded. In some subjects an additional electrode was inserted into the orbicularis muscle. In most cases the electrical activity of each muscle was displayed individually, but in others the electrical activity of agonist-antagonist was added together and then integrated. In two patients a retrobulbar injection of lidocaine (Xylocaine) was given in one eye, and in two others a van Lint lidocaine akinesia of the lids was produced. A Schiøtz tonometer or an electronic tonometer (with the electrical current in some cases on and in others off) with a 5.5 gm. weight was used for tonometry or tonography. The amplifier of the electronic tonometer, together with its attached recorder, was placed outside the shielded cage, and the wire connecting the electrically insulated tonometer hand piece with the amplifier was led into the cage by a small hole in the screen. The lids of both eyes were usually held apart by insertion of a

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From the Division of Ophthalmology, Department of Surgery, Stanford University School of Medicine. Department of Ophthalmology, Hadassah Rothschild University Hospital, Jerusalem (Dr. Kornblueth), and School of Optometry, University of California, Berkeley, Calif. (Dr. Marg).

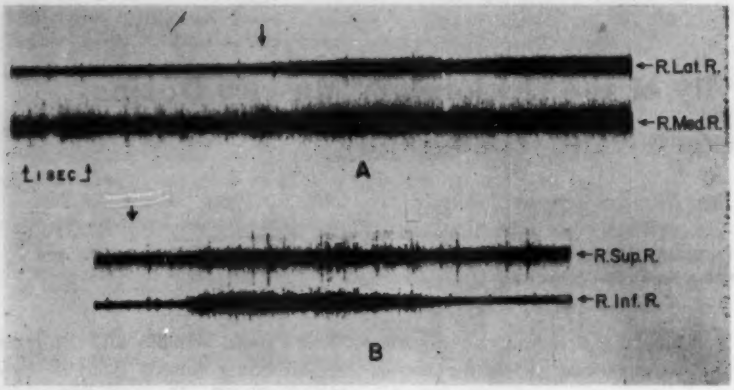

Fig. 1.—*A*, cocontraction of the horizontal recti of the right eye at the beginning of tonometry (arrow). *B*, the same for the vertical recti.

nonmagnetic speculum and occasionally merely by fingers. The tonometer was applied repeatedly on either eye and in some cases was held over but not on the cornea for a varying length of time. In a number of cases light or deep manual pressure causing several millimeters of enophthalmus was applied to the globe through closed lids.

Observations

Simply placing the tonometer in front of the eye or on the cornea resulted in increased electrical activity of all the extraocular muscles tested in all the patients (Figs. 1-3) except in those who were blind or nearly blind (Fig. 4) and for patients under general anesthesia. In all cases the

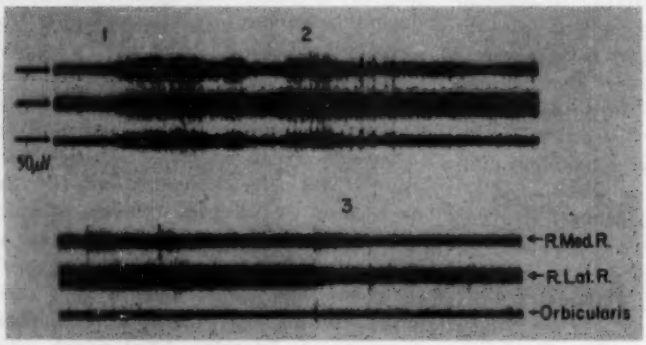

Fig. 2.—Cocontraction of the horizontal recti of the right eye and the orbicularis upon confronting the eye with the tonometer (*1*), placing the tonometer on the cornea (*2*), and removal of tonometer from the eye (*3*). Note that the orbicularis electrical activity falls off rapidly to the baseline level, while the cocontraction of the horizontal recti is maintained until the tonometer is removed from the eye. Also, note the decrease of the cocontraction of the horizontal recti upon removal of the tonometer.

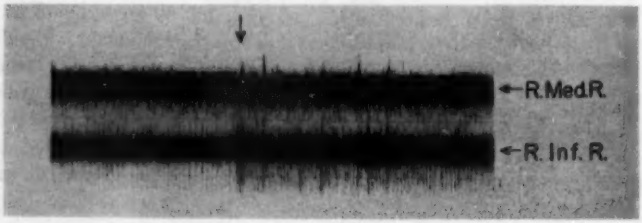

Fig. 3.—Demonstration of recruitment in the right inferior rectus with coactivity seen at the beginning of tonometry (arrow).

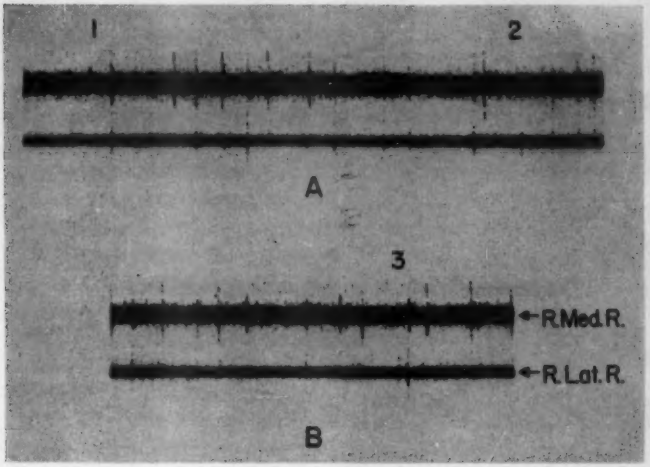

Fig. 4.—*A*, lack of response of recorded horizontal recti in a nearly blind patient on confrontation with the tonometer (*1*) and placing of the tonometer on the eye (*2*). *B*, again a lack of response of recorded activity of the same muscles in the same subject at the time of removal of the tonometer (*3*).

electrical activity of the muscles returned to normal on removal of the tonometer (Fig. 5). When a full four minutes of tonography was done it invariably resulted in an initial increase of coactivity of all the muscles in both eyes and became progressively smaller during the course of the measurement. Removal of the tonometer now resulted in a less observable decrease of the already gradually diminishing electrical activity (Fig. 6).

The increased electrical activity of the oculorotary muscles occurred simultaneously in both eyes (Fig. 7), i. e., the eye undergoing tonometry or tonography and the contralateral untested eye. It was of varying intensity and duration in different patients. It could be elicited in the same patient practically every time the tonometer was put near or on the cornea, though the intensity of the reaction varied from time to time.

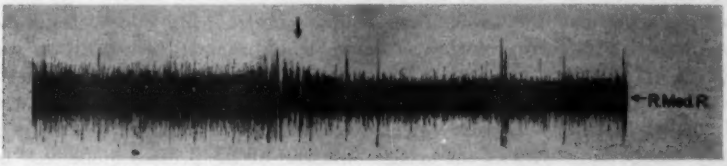

Fig. 5.—Note the marked decrease in activity of the recorded muscle when the tonometer is removed from the eye (arrow).

The invariable increase of the electrical activity of the oculorotary muscles was found to occur independently of the activity of the orbicularis muscle. In cases where

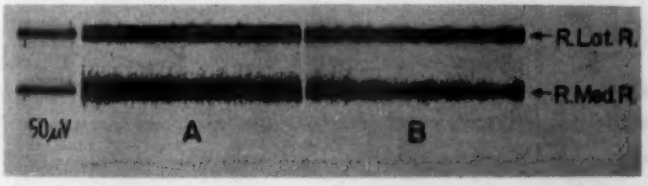

Fig. 6.—*A*, activity of the horizontal recti after three and one-half minutes of tonography and shortly before removal of the tonometer. *B*, the same recorded muscles immediately after removal of the tonometer. Note only slight decrease in the activity of the horizontal recti on removal of tonometer.

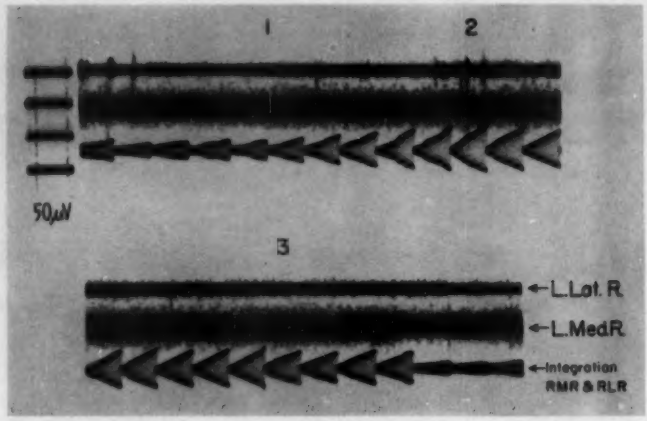

Fig. 7.—Increased coactivity of the horizontal recti in both eyes upon confrontation (*1*) and when the tonometer is placed on the cornea (*2*) and decreased coactivity of the horizontal recti of both eyes when the tonometer is removed from the eye (*3*). Tracing *3* is the added electrical activity of both horizontal recti of the right eye as recorded by an integrator. The height of the vertical step is proportional to the combined electrical activity of these muscles.

the orbicularis muscle was recorded in addition to the oculorotary muscles, it was found that on placing the tonometer in front of the eye the orbicularis activity sometimes, although not always, accompanied the response of the oculorotary muscles (Figs. 2 and 8).

Holding the tonometer over but not on the cornea for two and one-half minutes (Fig. 8) resulted in an increased electrical activity of the oculorotary muscles, which diminished gradually during this period but remained higher than its original level, without any change in activity of the orbicularis muscle. Akinesia of the orbicularis muscle did not prevent the reaction of the oculorotary muscles to tonometry or tonography.

A retrobulbar injection of lidocaine behind the eye undergoing tonometry did not interfere with the usual response of increased electrical activity of the oculorotary muscles in the contralateral eye.

Strong manual pressure on the globe through the closed lids to induce several millimeters of enophthalmus evoked increased electrical activity of the oculorotary muscles of the pressed globe only but with-

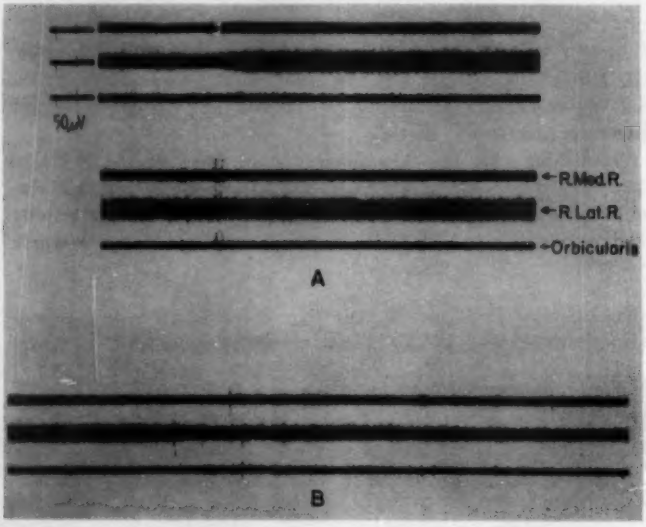

Fig. 8.—*A*, cocontraction of the horizontal recti without cocontraction of the orbicularis when the tonometer merely confronts the cornea within a few millimeters without being placed upon the eye at any time. *B*, the same as above approximately one and one-half minutes later, showing a gradual diminution of the coactivity of the horizontal recti.

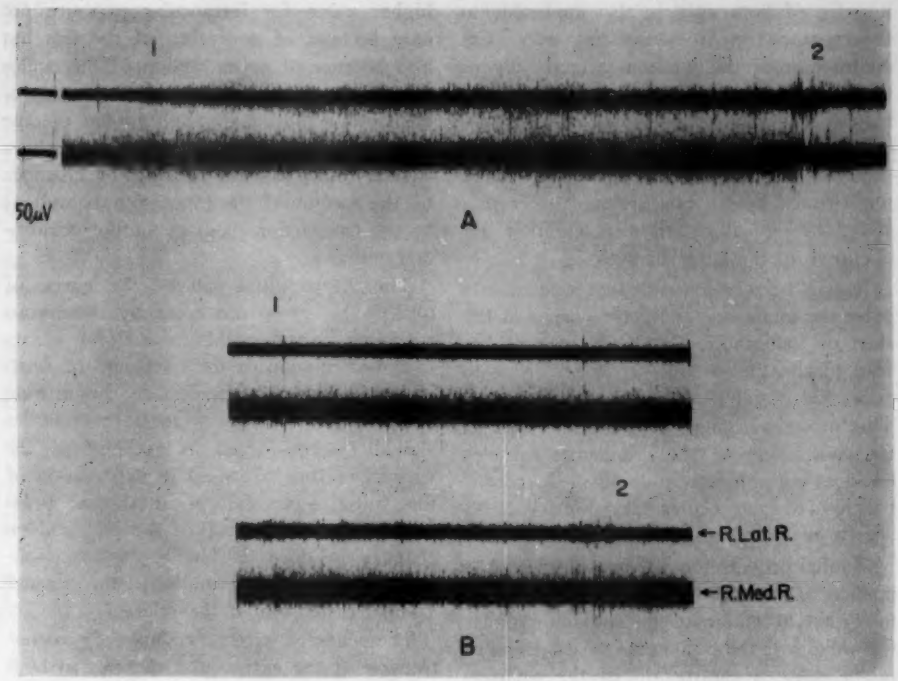

Fig. 9.—*A*, increased coactivity of the horizontal recti with strong enophthalmus-producing manual pressure on the recorded eye (*1*) and decreased coactivity upon release of this pressure (*2*). *B*, no response in the horizontal recti in same subject when similar pressure is made (*1*) and released (*2*) on the unrecorded eye.

out changes in the electrical activity of the fellow eye (Fig. 9).

Comment

The above results showed a marked increase of electrical activity of the oculorotary muscles due to a contraction of the muscles on routine tonometry and tonography. This cocontraction of the oculorotary muscles occurred simultaneously in both eyes and could be elicited from either eye on sudden placement of a tonometer near the eye and continued even when the tonometer was placed on the cornea. Vision is a prerequisite for the occurrence of this phenomenon, as it did not appear in blind or nearly blind persons or in patients under general anesthesia. In all other patients this so-called fright reaction, though of varying degree and of varying duration, could be evoked each time the tonometer was brought near the cornea. Patients with glaucoma, who were used to having their ocular tension taken repeatedly, showed the same responses. The intensity of the reaction seemed to diminish somewhat with repeated applications of the tonometer.

The orbicularis muscles participated frequently in this reaction but were not an integral part of it, as the cocontraction of the oculorotary muscles persisted after the orbicularis had relaxed or occurred occasionally without any contraction of the orbicularis muscles or after akinesia of the lids.

Retrobulbar injection of lidocaine behind the examined eye did not interfere with the occurrence of the so-called fright reaction in the contralateral eye, which is evidence for a central origin of this phenomenon. Apparently, Hering's law of equal distribution of nerve impulses to the oculorotary

muscles of both eyes is also applicable to the cocontraction in nonrotating eyes. Cocontraction of the horizontal recti only in the stationary eye was described in asymmetric convergence,[6] in which case the cocontraction was one-sided and the remaining oculorotary muscles in the same eye were not affected by it. For this and other reasons,[6] the so-called fright reaction is not operative in the latter instance.

It has been suggested that one should poise the tonometer above the cornea at the start of tonography for 10-20 seconds before placing it on the cornea, in order to avoid the initial protective blepharospasm.[7] This procedure might exclude the effect of the contraction of the orbicularis muscles but does not appreciably diminish the cocontraction of the oculorotary muscles, as shown in our cases.

Manual pressure of different degrees was applied to the globe through the closed lids in order to eliminate the possibility that the weight of the tonometer by its pressure might cause a contraction of the oculorotary muscles when placed on the eye. It was found that gentle pressure (equivalent or greater than the tonometer weight) showed no demonstrable change in the activity of the muscles. Fairly strong enophthalmus-producing pressure evoked a cocontraction of the muscles which was limited only to the side of the pressed globe. This unilateral cocontraction consequent to the enophthalmus produced by pressure was apparently a local peripheral adjustment of the oculorotary muscles to take up the slack of the muscles. No such reaction occurred with nasal or temporal displacement of the globe in a similar manner.

How could cocontraction of the oculorotary muscles affect the measurements of tonometry and tonography? There is ample clinical and experimental evidence to show that relaxation of the oculorotary muscles causes a decrease[3,8-11] and their contraction an increase in intraocular pressure.[12-16] It is interesting to speculate that the first reading with the tonometer might give a higher value for intraocular pressure not only because of squeezing of the lids but also because of cocontraction of the oculorotary muscles. The massage effect produced by additional applications of the tonometer might be caused by pushing aqueous humor out of the anterior chamber by the weight of the tonometer as well as by the contraction massage of the oculorotary muscles.

The steep initial fall of the curve of tonography was observed by numerous authors[17-19] and could account for errors in the calculation of the coefficient of facility of outflow. A progressively diminishing contraction of the oculorotary muscles should be considered in addition to the various reasons proposed in explanation of this initial steep fall in intraocular pressure, such as squeezing of the lids, sudden changes in diastolic blood pressure, sudden changes of blood volume of the eye and gradual distension of the sclera.

The massage effect produced by cocontraction of the extraocular muscles in both eyes might be an auxiliary factor for the occurrence of the so-called ophthalmotonic consensual reflex, where the tonographic procedure in one eye induces a decrease in intraocular pressure of the other eye.[20]

Without detracting from the relative accuracy of tonometry this study calls attention to a possible additional source of error in the calculation of the intraocular pressure imposed by placing the tonometer on the eye.

Summary

Electromyographic studies were performed to show the effect produced on the oculorotary muscles by tonometry and tonography. It was found that holding the tonometer near or on the eye consistently caused a cocontraction of the oculorotary muscles which was simultaneous in both eyes. This reaction was not necessarily accompanied by a contraction of the orbicularis muscles and occurred also after akinesia of the lids. The occurrence of this response, a so-called protective or fright

reaction which is of central origin, was dependent on sight, as it did not occur in blind or nearly blind subjects and in patients under general anesthesia. Tonography showed an initial cocontraction of the oculorotary muscles which diminished progressively over the course of four minutes. It is suggested that the changes in the tonus of the oculorotary muscles caused by placing a tonometer near or on the eye may alter the intraocular pressure in both eyes and introduce some inaccuracies in tonometry and tonography.

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Viral Studies of the Normal Eye

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The medical literature has reflected an increasing interest in viral diseases of the eye.[1,2] While many of the reports concern the clinically diseased eye, little attention has been directed to the viral flora of the normal conjunctival sac. The bacterial flora of the human eye has been studied extensively, and such information is important in evaluating microbial disease of the eye.[3,4] It is equally significant to ascertain a base line of the normal viral flora of the human eye. This report concerns such a study on 200 eyes.

Materials and Methods

The clinically normal eyes of 100 persons were investigated for the presence of virus in the conjunctival sac. Patients coming to the Outpatient Eye Clinic of the University of Texas-Medical Branch Hospitals were chosen. The eye patients were chosen because the specimens could be taken as routine on the new patients with a minimum of time and explanation, as the actual brisk swabbing of the conjunctival sac proved uncomfortable. A local anesthetic was not used, since this might prove an added toxic factor on the inoculated tissue cultures. Only those patients with normal-appearing conjunctiva and cornea and without a history of recent eye inflammation were chosen. Ages of the patients ranged from 9 months to 87 years; the number in each decade was equally distributed, as far as possible.

Collection of Specimens

A small sterile cotton swab on a wooden applicator was used, the same one used for the lower conjunctival fornix of each eye. For the first few specimens the upper palpebral conjunctival area was also swabbed, but this proved too irritating. The swab was moistened with Hanks' solution, and, while carefully avoiding the eyelashes, the conjunctiva was swabbed with a firm stroke, firm enough to remove the occasional epithelial cell. The swab was placed immediately in a screw-capped sterile tube which contained 0.5 ml. of Hanks' solution. If tissue culture cell sheets were available the inoculation of the specimen was done immediately. Otherwise the specimen was sealed in an ampoule and placed in the dry ice box, remaining there until the tissue culture tubes were ready for inoculation. All transferring or inoculation was done within 30 minutes to 2 hours from the time of collection of the specimen. All procedures were performed in a room of the laboratory which was not used for any virus work other than this study. Sterile technique was used at all times. Prior to this study, to check the technique of swabbing and preserving, specimens were taken from the conjunctiva and cornea of an eye with a typical dendritic ulcer. After primary inoculation into tissue cultures and on subsequent passages this specimen showed cytopathology typical of herpes simplex virus.

Tissue Culture Techniques

The cell line used for the inoculation of the first 25 specimens was human amnion. This cell line was prepared from fresh human amnion with use of a technique similar to that of Zitcer et al.[5] This proved a successful method but without assistance a very time-consuming one. Subsequent studies of 75 specimens were performed with trypsinized monolayers of monkey kidney cells.*

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The University of Texas-Medical Branch.

* Microbiological Associates, Bethesda, Md.

The latter cell preparation was chosen for its wide viral sensitivity range, its availability through commercial channels, and its hardiness.[6,7] Prior to inoculation, the cell sheets were washed three times with Hanks' solution and then 0.1 ml. of each specimen was inoculated into three tubes and 1.0 ml. of maintenance medium added. (Since the volume of the original specimen was only 0.5 ml., each specimen provided only three to four tubes for investigation.)

The maintenance medium consisted of Parker's Medium 199 containing 2% normal calf serum, plus 100 units of penicillin and 100μg. of streptomycin per milliliter.[8,9] This nutrient medium was adjusted to pH 7.3 with 2.8% $NaHCO_3$. The treated tissues and controls were incubated in stationary racks at 36 C. They were examined microscopically every 24 hours for areas of cytopathology, or cytopathogenic effect (CPE). The medium was changed on the third day, and thereafter only pH adjustments were made when necessary. All cultures with negative CPE were examined for 21-27 days. They were then frozen, thawed, and passaged blindly to fresh cells. The cultures which showed cytopathology were frozen at −20 C in order to release intracellular virus from the lysed cells.

Passaging

All specimens were passaged at least once. The frozen cultures were thawed rapidly in the 36 C water bath, and cell remnants were scraped loose from the tube wall by means of a sterile wire loop. The contents of three or four culture tubes from each inoculum were pooled. This was clarified at low speed centrifugation, and 0.1 ml. of the supernatant fluid was inoculated into at least three fresh tubes of monkey kidney-cell cultures. The maintenance medium was the same as that noted above. The tissue in each tube was subsequently examined for 14 days, and each was passaged again if a CPE appeared.

Changes Observed in the Cell Sheets

Careful control of the pH of the cultures and changing of the nutrient medium were required to maintain tissue culture cells in a healthy state for three or four weeks. In this study cells of the same age varied in their appearance. When the cells are in an unhealthy state it is difficult to distinguish between cytopathology changes due to a virus and those due to nutritional difficulties, pH variability, and unknown toxic factors.[10] For this reason the specimens showing any questionable cytopathology were carried through further passages. Even when the occasional control tube showed a similar poor condition in the cell sheet, both specimen and its control were passaged to determine if contamination had occurred in the control or if another factor was responsible.[11]

Changes suspected of being cytopathologic due to a virus included swelling of individual cells, often in a relatively small area of the cell sheet and usually before the fifth day. Small shrunken cells was a later feature; this was frequently seen, involving a larger area. Even the controls occasionally had areas of small shrunken cells. In a few specimens actual clumping of the cells with spaces in the cell sheet was seen as an even later feature, and in 24 to 48 hours the areas of clumped cells loosened from the glass. At no time were giant cells or a syncytium of cells seen in any culture.

A branching appearance was a rather prominent finding in many cultures of inoculated monkey kidney cells after several days, sometimes in the 14-27 day period.[12] At first it was thought that this could be a pathological change even when observed in the control in a few cases, possibly due to an agent in the monkey kidney cell itself.[11] However, as more tubes of cells were examined, many uninoculated cultures were found to have this branching area at the edges of the cell sheet, the stretched cells reaching to the next similarly stretched cell. With passage, the branching appearance was

not found consistently, and the conclusion was reached that this may be a nonspecific change of aging monkey kidney cells.

Results

From the initial inoculation there were 23 specimens in which one or more tubes showed changes in the cells. Most of these were considered to be changes possibly due to nutritional disturbances. A careful study of the subsequent passage of these 23 specimens revealed only 10 which showed any cell change and then not necessarily the same as in the original. However, in the first passage 17 additional specimens had cell changes that were not observed in the initial inoculation. Again most were attributed to nutritional factors.

All the 23 specimens from the initial inoculation and the 17 from the first passage were again passaged. In this second passage only 10 specimens showed any changes in one or more tubes but never all the eight tubes of each specimen. Still no definite cytopathology, such as giant cell or syncytium formation or lytic activity, was observed. Five of these ten were of the original inoculation only, and five were common to the original and first passage.

All 10 were passaged, each into 10 tubes of tissue culture. From this third passage only three specimens had vague cell changes consisting of swollen cells in one area of a tube. The third passage was observed for 10 days.

A fourth passage was done on the three specimens, inoculated onto carefully examined, healthy monkey kidney-cell cultures. There were no cytopathic changes noted in any of the 10 tubes of each of the three specimens, observed for 10 days.

Examination of the accumulated data fails to indicate that an agent was recovered from any of the 100 specimens.

Comment

The methods and technique used were checked by means of an inoculum collected from a recognized dendritic ulcer, which in initial and subsequent passages gave cytopathology typical of herpes simplex.[10] However, in such a case there is more conjunctival discharge than in the normal sac, and this in turn may give a higher concentration of the agent on the swab. The swabbing of the normal sac was done so that epithelial cells were included in the test specimen.[13] If a viral agent was present in the "normal eyes," its concentration may have been too low for the sensitivity of our test system. All specimens were passaged at least once after an interval of 14-27 days, and the results again supported the negative findings of the first passage. The tissue culture system employed in this study was sensitive to herpes virus and to adenoviruses, as tested in another laboratory room.

This study has not revealed a "masked" locus of adenovirus in the conjunctiva, as has been demonstrated in adenoid tissue.[14] Further search will be needed to trace the source of adenovirus Type 8, which is associated with the syndrome of epidemic keratoconjunctivitis.[15]

There was some difficulty in maintaining each of the 400 tissue culture cell sheets for the initial and again for the first passage series in the same healthy state. This is why further passages were necessary to definitely rule out cytopathology due to a viral agent. Perhaps the cultures should have been observed for longer than 21-27 days in the initial passage, although most known viruses which are associated with the eye show activity within that time and usually in the first passage.

The vague changes in the cell sheets seem to indicate the influence of factors, toxic or otherwise, which show up in some cultures and not in others. Since on freezing, thawing, and repassaging of these cultures such variations in appearance of the cell sheets were not reproduced, this suggests that the minor changes were not due to a viral agent.

Summary and Conclusion

The study of the normal conjunctiva of 100 persons gave no indication that there

is any virus present. Conventional tissue culture methods were used in the investigation. Trypsinized monolayers of human amnion cells and monkey kidney cells were found to be suitable for such a study.

The Departments of Ophthalmology and Preventive Medicine of the University of Texas-Medical Branch cooperated in this study. The study was made possible through financial assistance from the Medical Research Foundation of Texas and from the James McLaughlin Fellowship Fund.

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Intracavernous Aneurysms of the Internal Carotid Artery

Their Clinical Features and Natural History

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In 1872, Roberts Bartholow, of Cincinnati, wrote a description of the clinical features of intracranial aneurysms arising from the internal carotid artery, which showed evidence of acute clinical observation. Jonathan Hutchinson, a London surgeon, described a case in 1875, and even considered carotid ligation. More recently, McKinney, Acree, and Soltz (1936) reported the clinical and radiological features of eight cases and called attention to the erosion of the optic foramen and widening of the superior orbital (sphenoidal) fissure which occurred in several of them. Jefferson (1938) made a detailed study of the clinical features of a series of 17 cases, which forms the basis of our present knowledge. At this period arteriography was in its infancy. Since then, relatively safe percutaneous angiography has become available and was undertaken in the majority of the present series of 15 patients which form the basis of the present contribution.

Aneurysms arising from the internal carotid artery as it traverses the cavernous sinus behave differently from aneurysms arising elsewhere in the skull by virtue of their position. They arise from a large artery without any large branches as it traverses a venous sinus and tend to present themselves to ophthalmologists on account of ocular features.

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Rupture may certainly occur but into the cavernous sinus rather than into the subarachnoid space, so that instead of the usual subarachnoid hemorrhage, with its 40% to 50% mortality, the patients develop exophthalmos, which may be unilateral or bilateral, accompanied by a bruit audible over the eye and head. Life is preserved at the expense of the eye. If rupture occurs, it seems to happen early in its course and before the aneurysm has filled up the cavernous sinus, for prerupture symptoms are unusual.

As the main purpose of this contribution is to describe the clinical features and course of unruptured intracavernous aneurysms, I shall only refer briefly to the fistulous carotid-cavernous aneurysms. While they are the result of head injury with traumatic disruption of the wall of the carotid artery in the cavernous sinus, they may also arise spontaneously, and especially in middle-aged women. In this case, they are probably due to rupture of a small aneurysm, or to atherosclerosis, or to both, though postmortem examinations are scanty. Symptoms are usually of abrupt onset, with the appearance of a cephalic murmur, as a rule audible to the patient, and often abolished or diminished by digital carotid compression in the neck. Pain may be present at the onset but is often absent, and loss of consciousness is unusual. Exophthalmos develops either suddenly over the course of a few days, or gradually over a period of some weeks. It is usually unilateral and on the side of the fistulous communication, but it is sometimes bilateral and occasionally more

marked on the contralateral side. Communication between the two cavernous sinuses is responsible for the bilateral exophthalmos and probably the degree of communication varies in different persons. The conjunctiva usually shows evidence of marked vascular congestion, often a striking feature, and chemosis and edema of the eyelids may be severe. When the exophthalmos is bilateral and severe, the clinical picture may closely resemble that of severe endocrine exophthalmos, except for the presence of a cephalic murmur and marked congestion of the conjunctival vessels. Pulsation of the eye may be present but is often difficult to see. An ocular palsy is common, especially a sixth nerve palsy, and a total bilateral ophthalmoplegia is sometimes seen in cases with bilateral exophthalmos. Involvement of the trigeminal nerve may occur but is rarely severe. Ophthalmic herpes occurred in one patient. Many cases show no evidence of failure of vision, but progressive optic atrophy and evidence of retinal venous occlusion have been recorded. The clinical course is by no means uniform. Some appear to reach a state of equilibrium and live for years. Spontaneous thrombosis with recession of the exophthalmos but with loss of vision has been recorded. Common carotid ligation in the neck should be seriously considered, especially if the exophthalmos is progressive and in the cases in which exophthalmos is bilateral. A remarkable improvement often occurs in the latter group.

Unruptured Intracavernous Aneurysms

If rupture does not occur, the aneurysm appears to enlarge fairly quickly, so that it soon fills the cavernous sinus. This provides an added dural coat for the aneurysm which seems to slow down further expansion and act as an added protection against rupture. Rupture is certainly unusual once the aneurysm has filled the sinus. Further expansion may occur, however, usually in a gradual manner over a period of several years. The aneurysm may even strip up the dura of the middle fossa and present as a large mass stretching from the superior orbital (sphenoidal) fissure to the petrous portion of the temporal bone, lateral to the sella (Fig. 1). Anterior expansion often erodes the optic foramen and widens the superior orbital (sphenoidal) fissure, causing compression of the optic nerve and exophthalmos. Expansion posteriorly may erode the petrous portion of the temporal bone and inferiorly erode the floor of the middle fossa. Inward extension may cause radiological changes in the sella.

A laminated clot is often laid down in the walls of the aneurysm; complete thrombosis may occur, with spontaneous cure, leaving in its wake some loss of function of the eye, either vision or motility.

Clinical Features

The clinical features to be described are based on 15 cases of unruptured intracavernous aneurysm, which have been followed up for several years.

All except two of the patients were women, a striking fact, and all except four patients were over the age of 50 years at the time of onset of symptoms. Only one started with symptoms under the age of 40 years, so that these aneurysms are seen chiefly in middle-aged or elderly women.

The onset of symptoms is occasionally abrupt, but it is often slow and insidious, with occasional bursts of activity during which there may be severe pain in and around the eye, often with an increase in the ocular palsy, which is present in almost all cases. In some cases the clinical condition appears to be relatively static for long periods, suggesting that expansion has slowed down or even ceased.

Pain in and around the eye, and in the face, is sometimes a prominent symptom and tends to occur in bouts, leaving the patient relatively free in the interval. In many cases, however, pain is a relatively minor symptom especially in the early stages. Several patients had no pain for several months or years after the onset of

Fig. 1. — Large intracavernous aneurysm occupying inner part of middle fossa of skull (See also Fig. 9).

an ocular palsy, and one patient has had little or no pain to date, 10 years after the onset and without pain was the sole clinical one-third of the total, was pain a prominent symptom in the early stages.

Ocular Palsy.—As might be expected from the anatomy of the cavernous sinus, involvement of the oculomotor nerves is usually one of the presenting clinical features. The sixth nerve, being in closest relationship with the internal carotid artery, is usually affected first. In one patient, a unilateral sixth nerve palsy of abrupt onset and without pain was the sole clinical manifestation of an intracavernous aneurysm for no less than eight months. After this period, an almost total unilateral ophthalmoplegia appeared abruptly over a period of a few days, accompanied by severe pain and involvement of the trigeminal nerve.

Eventually, involvement of the third cranial nerve also appeared in all cases, with one exception, though it may not be evident for a year or more after the onset of symptoms (Fig. 2).

A point of interest is that the pupil is usually small, probably on account of coincidental involvement of the ocular sympathetic fibers surrounding the internal carotid artery.

Trigeminal Sensory Loss.—Involvement of the trigeminal nerve is usually regarded as one of the classical signs of these ex-

Fig. 2.—Total ophthalmoplegia due to unruptured intracavernous aneurysm.

panding intracavernous aneurysms. The ophthalmic division is especially liable to be affected, with consequent impairment or loss of corneal reflex, but all three divisions may be involved, including the motor division.

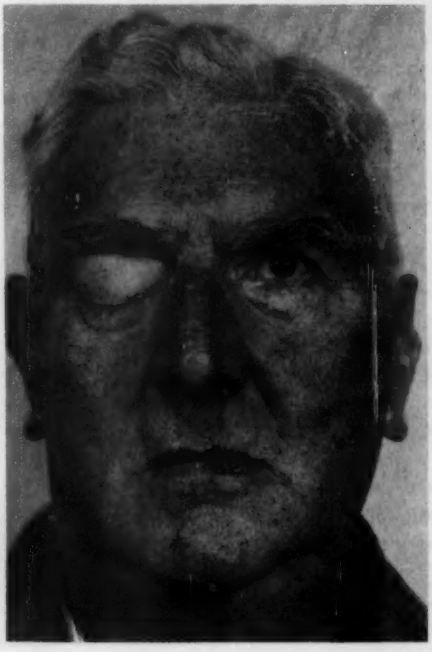
Yet trigeminal sensory loss cannot be regarded as a *sine qua non* in diagnosis. It often appears late in the clinical evolution, and severe sensory loss is unusual. From a study of the clinical chronology of the present series of 15 patients, one-third had no evidence of trigeminal sensory loss 8 to 12 years after the onset of symptoms, one-third developed sensory loss more than 3 years after the onset of symptoms, and in only 5 cases was there evidence of trigeminal sensory loss within 2 years of the onset.

Exophthalmos and Optic Atrophy.—Aneurysmal expansion in an anterior direction may occur severely over a period of several years, causing erosion of the optic foramen and widening of the superior orbital (sphenoidal) fissure visible on radiological examination. Clinical evidence of anterior expansion consists of exophthalmos and ipsilateral visual failure due to compression of the optic nerve in the optic canal. Either exophthalmos or visual failure may appear first, but eventually both usually appear.

Unilateral exophthalmos occurred in more than half the present series (9 out of 15 cases). It is usually moderate in degree and a fairly late phenomenon. It may be masked, to some extent, by the presence of ptosis, consequent on involvement of the oculomotor nerve (Fig. 3). In two patients, the exophthalmos was severe and in one, no less than 12 mm. in degree, so that a diagnosis of orbital tumor was considered at one stage. The exophthalmos is quite unlike that seen in the fistulous carotid-cavernous aneurysms, in that there is no chemosis or edema of the lids and no congestion of the conjunctival vessels.

Compression of the optic nerve by anterior expansion of the aneurysm causes

Fig. 3.—Ptosis and ocular palsy with marked exophthalmos.



progressive loss of vision of the ipsilateral eye, followed by optic atrophy. This occurred in 6 of the present 15 cases. It is usually a late phenomenon and is accompanied or preceded by exophthalmos. In one patient, a woman of 58 years, unilateral visual failure and optic atrophy was the sole presenting feature. There was no headache or pain, no ocular palsy, and no exophthalmos. Vision was reduced to 6/18 in the affected eye, and the visual field showed loss of the temporal and upper nasal field, the only intact vision being in the lower nasal field. Erosion of the optic foramen and widening of the superior orbital (sphenoidal) fissure was seen on radiological examination, and arteriography revealed a large intracavernous aneurysm. All this was 10 years ago. The patient is still fit and well, apart from her unilateral visual impairment, but has recently developed an ocular paresis and slight exophthalmos; calcification has appeared in the wall of the aneurysm.

Posterior Aneurysmal Expansion.—In some cases, expansion may extend posteriorly as far as the petrous portion of the temporal bone. Involvement of the internal auditory meatus and acoustic nerve is possible and would seem to be a likely cause of the ipsilateral deafness which is sometimes encountered as a late phenomenon. Three of the present series of fifteen patients had ipsilateral deafness, and three further patients had bilateral deafness.

Cephalic Murmur.—In spite of the large size which these aneurysms may attain, a cephalic murmur is unusual and occurred in only 2 out of 15 patients. The bruit ceased after carotid arteriography in one and after common carotid ligation in the other.

Vascular Hypertension.—About half of the present series had vascular hypertension, and this, together with atherosclerosis, is probably one factor in pathogenesis.

Of seven hypertensives, five died from cardiac failure or cerebrovascular accidents, 5 to 10 years after the onset of symptoms. One patient is still alive 11 years after the onset, with a blood pressure reading of 245/120. Of the eight nonhypertensives, five are still alive, 8 to 11 years after the onset, and two died, 17 and 20 years after the onset. Normal blood pressure is indicative of a better prognosis.

Prognosis

Fourteen of the fifteen cases have been followed up to date. Six are still alive and well, apart from an ocular palsy or loss of vision, 8 to 11 years after the onset of symptoms. Only one of these had severe hypertension (240/140).

Seven patients have died, 5 to 20 years after the onset, chiefly from cardiac failure or cerebrovascular accidents. Most of these had vascular hypertension. One patient is still alive with a hemiplegia which followed internal carotid ligation performed 18 months after the onset. One patient is untraced.

Thus many of these patients are able to live a fairly active life for a considerable number of years with an ocular palsy or unilateral visual loss.

Radiological Changes in the Skull

Careful radiological examination of the skull and optic foramina may contribute materially to the diagnosis. As the aneurysm extends in all directions, special attention should be paid to the optic foramina and superior orbital (sphenoidal) fissure, the sella, the petrous part of the temporal bone, and the floor of the middle fossa for evidence of erosion. Furthermore, these aneurysms have a particular tendency to show evidence of calcification in their walls.

Calcification in the walls appears gradually and probably takes several years to develop. It is seen as an intermittent or continuous curvilinear calcification above and lateral to the sella and may finally form a complete or incomplete circle, with the sella showing through in the center in the lateral view (Fig. 4). It occurred in 8 of the present 15 cases, and in 5 of these

Fig. 4.—Ptosis and ophthalmoplegia, with marked exophthalmos (See also Fig. 10).

calcification was not seen in the earlier radiological studies but became evident between four and seven years after the onset of symptoms.

Erosion of the lower and outer rim of the sphenoidal fissure is a particularly common feature in these cases, due to anterior extension of the aneurysmal wall, and occurred in 8 of the present 15 cases, usually in association with exophthalmos or compression of the optic nerve, or both. Further erosion may cause widening of the superior orbital (sphenoidal) fissure, which appears to coalesce with the optic foramen (Figs. 5 and 6). This erosion appears to have been first described by McKinney, Acree, and Soltz, in 1936, and by Jefferson, in 1937. More recently, Rischbieth and Bull (1958) have reviewed these radiological features.

Destructive changes are sometimes seen in the sella itself, which may be enlarged, with erosion of the anterior clinoid process and of the dorsum sellae. Erosion of the floor of the middle fossa was seen in one patient, and erosion of the petrous part of the temporal bone in another.

Arteriography.—Percutaneous arteriography was performed in 13 of the 15 patients which form the basis of the present study. Of the two patients who did not have arteriographic studies, one had a calcified ring shadow on one side of the sella, and the other came to postmortem examination, with visible proof of a large intracavernous aneurysm occupying the medial half of the middle fossa of the skull.

In all 13 cases, with one exception, the aneurysm filled and was usually of considerable size, often obliterating the outline of the sella in the lateral view (Figs. 7 and 8).

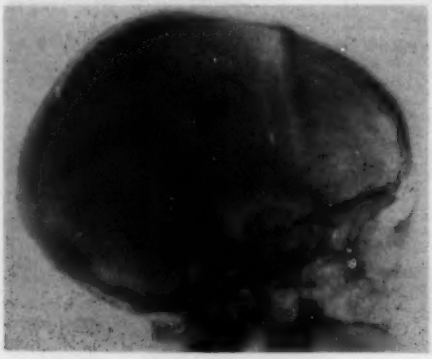
Fig. 5.—Normal optic foramen (*R*).

Fig. 6.—Erosion of optic foramen (*L*) by aneurysm.

In one case, the radiopaque shadow was considerably smaller than the calcified ring shadow which was present, indicating a considerable layer of clot in the wall.

In only one case was there lack of filling of the aneurysm, which was calcified. The radiopaque material showed a block of the internal carotid artery shortly above the carotid bifurcation, and it seems likely that in this patient, whose history went back for about 17 years, spontaneous cure had occurred by thrombosis in the aneurysm and internal carotid artery.

Fig. 7.—Arteriogram showing aneurysm filled with radiopaque substance (Lateral view with sella showing through in center).



Treatment by Carotid Ligation

Ligation of the common carotid artery in the neck was undertaken in five patients without any complication, such as hemiplegia. This seems to be the operation of choice, provided the patient can stand

Fig. 8.—Arteriogram (*P. A.* view).

digital compression of the carotid artery in the neck for 10 to 15 minutes without untoward effect, and provided that cross flow arteriographic studies show that there is adequate filling of the middle and anterior cerebral arteries on the side of the aneurysm from the internal carotid artery of the opposite side. Of the five patients in whom common carotid ligation was performed, three are still alive and well, 7, 10, and 10 years later, and two have died from cerebrovascular accidents and cardiovascular degeneration 7 years after ligation.

In two patients, ligation of the internal carotid artery was performed, with disastrous results. Both developed a hemiplegia, and one died 12 days later.

Each case must be judged on its merits, bearing in mind that many of these patients are over 60 years of age and are often the subject of atherosclerosis, which may cause defective collateral circulation with added risk on carotid ligation. The natural history of untreated aneurysms has also a bearing on the problem, as some patients may live for many years without surgical interference. Of the present series, eight patients had no surgical interference. Three of these died from 5 to 9 years after the onset, two died from 17 to 20 years after the onset, two are alive and well 10 to 12 years after the onset, and the fate of the remaining case is unknown.

It is my view that common carotid ligation should be seriously considered in patients under the age of 60 years, who have severe pain, failing vision or exophthalmos, provided cross flow studies are satisfactory.

Postmortem Examinations

In two cases which came to postmortem examination, there was in each case a large aneurysm occupying the medial portion of the middle fossa, and laminated clot had considerably reduced the size of the aneurysmal cavity in each case (Fig. 9; also Fig. 1). One patient died five years after the onset of symptoms with no surgical treatment. The second patient died eight years after the onset of symptoms; internal carotid ligation had been performed 12 days before death.

In both cases, erosion of the optic foramen and superior orbital (sphenoidal) fissure had occurred. Inspection of the orbit from the front in the second case showed bulging of a mass of connective tissue and fat through the superior orbital fissure, which was severely eroded, and behind this was the aneurysmal wall (Fig. 10).

In both cases, other intracranial aneurysms were present; in one patient a bilateral middle cerebral aneurysm, which had ruptured into brain substance and caused

Fig. 9.—Section across aneurysm shown in Fig. 1, containing laminated clot.

Fig. 10.—Orbit front showing erosion by aneurysm (See Fig. 3).

death, and in the second patient an old thrombosed aneurysm of the basilar artery.

In a third case, the aneurysm was small and thick-walled. It did not form a large mass in the middle fossa and was hardly visible until the cavernous sinus was sectioned transversely. This patient died of cardiac failure and cerebrovascular accident, unconnected with the aneurysm, 10 years after the onset of symptoms. Common carotid ligation had been performed three years after the onset of symptoms. Both common and internal carotid arteries on the side of the ligation were completely occluded by thrombosis, and the internal carotid artery contracted to about half its normal size. The latter artery was also thrombosed as it left the aneurysmal sac, up to the level of the posterior communicating artery. It seems likely that common carotid ligation had a beneficial effect on the aneurysm by slowing down and diminishing the blood supply, for the aneurysm was considerably smaller than had been expected from the original arteriographic studies performed seven years previously, before carotid ligation was undertaken.

Prof. William Blackwood, of London, supplied details of three postmortem examinations and material for Figures 1, 9, and 10. Dr. Hugh Davies and Dr. William Bull, of London, performed radiological and arteriographic studies.

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Hereditary Alkaptonuria with Ochronosis

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Ochronosis is a rare condition in which eye findings are almost always present.[1] This disease has not been stressed in ophthalmological literature, but its detection is a matter of considerable importance. Skinsnes[2] reported a tragic case where a man's only eye (the other one was lost after an injury) was needlessly removed because of suspected melanoma of the uvea. This eye had medial and lateral pigmentations of the globe such as are found in ochronosis. No tumor was found. The patient died one year later of bronchopneumonia, and the diagnosis of ochronosis was proved at autopsy.

Hereditary alkaptonuria is characterized by the excretion of homogentisic acid in the urine because of a block in the metabolic breakdown of tyrosine to carbon dioxide and water.

phenylalanine
↓
tyrosine
↓
homogentisic acid
↓
acetoacetic acid
↓
CO_2 and H_2O

There may be no symptoms, but about one-half of the cases have deposition of considerable amounts of pigment in the tissues, called ochronosis. This disease may develop as early as the third decade of life[1] and presents itself as a triad of (1) pigmentation of the ears and sclera, (2) urine that darkens on exposure to air, and (3) osteoarthritis.

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Report of a Case

A 59-year-old white woman was first seen at the Illinois Eye and Ear Infirmary on Nov. 18, 1957, with the complaint of blurring for near vision. She also mentioned the presence of dark spots on both eyes which were initially noticed by her daughter five years previously and which had not changed since then.

The appearance of both eyes was practically identical. The corrected vision was 20/20 in each eye, wearing R. E.: +1.00 +1.50 ax. 180 degrees; L. E.: +1.00 ax. 175 degrees; add +2.25=four-point type. Tension was 11 mm. Hg in each eye. The scleras showed oval, diffuse slate-gray areas of pigmentation bilaterally, temporal to and 2-3 mm. from the limbus within the area of the palpebral aperture (Fig. 1). There was also a smaller, less deeply pigmented, similarly situated spot nasal to the limbus in the left eye. Biomicroscopic examination of the conjunctiva near the limbus within the palpebral fissure revealed scattered, round, golden-brown deposits which looked like discrete drops of lipid (Fig. 2). Some of these globules were very dark, and others were almost transparent. The corneas appeared normal grossly, but the biomicroscopic findings were most interesting. Numerous tiny round golden-brown droplets similar to those seen in the conjunctiva were visible at the level of Bowman's membrane near the limbus within the palpebral fissure. A few much larger clusters were also present (Fig. 2). The remainder of the eye examination was normal.

The patient was a proven diabetic, controlled on diet alone. Systemic review was

Fig. 1. — Ochronotic pigmentations are visible in the sclera of the palpebral fissure area.

negative except for backache, rigid spine, and pain with swelling of the left knee. The patient mentioned that if she soiled her underclothing with urine it left a dark stain. Her mother, now dead, also experienced dark staining of undergarments by urine but was not troubled by arthritis or pigmentation of her eyes. The patient's three children and a sister, her only sibling, were all normal. The family history was otherwise negative for ochronosis, arthritis, or diabetes; her parents were not consanguinous.

On physical examination the patient had Heberden's nodes on the middle finger of each hand, swelling and limitation of movements of the left knee, and a rigid spine. Both ears were firm and thickened, and the cartilages of the concha and antihelix were a rather dark bluish-gray color. The eyelids, nose, and skin of the cheeks appeared to have normal coloration.

X-ray studies showed nonspecific osteoarthritic changes in several joints, but the lumbodorsal spine presented the classical ochronotic findings [3] of thinned and calcified intervertebral discs with some ligamentous calcification (Fig. 3). The glucose-tolerance test demonstrated a definite diabetic type curve. The urine turned very dark on stand-

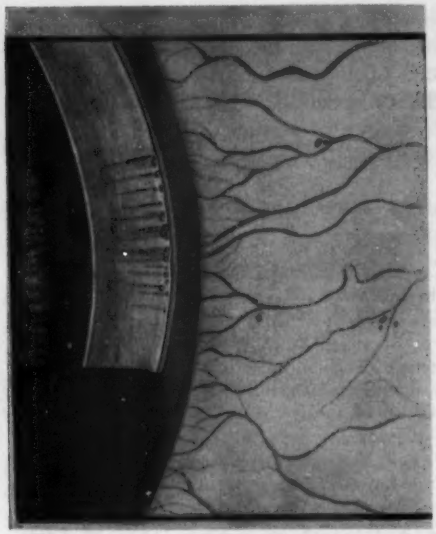

Fig. 2.—Golden brown deposits are seen in conjunctiva, particularly near vessel bifurcations and in cornea near limbus, at Bowman's level.

ing or after the addition of 10% sodium hydroxide solution. A single drop of alkalinized urine placed upon exposed photographic paper caused the paper to turn dark within seconds (Fig. 4) (positive Fishberg test).[4]

Comment

This disorder shows a familial tendency,[1] usually inherited as a recessive Mendelian characteristic but occasionally dominant. Virchow named the disease, in 1866, after microscopic observation of tissue containing ochre-colored pigment granules. Osler,[5] in 1904, described the clinical features of the disease including the eye findings. The incidence of alkaptonuria has been stated by Stern[6] to be approximately 1/1,000,000 population, and ancestral consanguinity is present in 30% of cases. The sex ratio is 2:1, males being affected more commonly. The disease is rarely found among Negroes. One may obtain a history of dark-staining diapers during infancy.[7] Homogentisic acid does have reducing properties, and some persons have been refused life insurance because their urine tested positive for "sugar."

Grayish-blue pigment is deposited most abundantly in parts of the body characterized by scanty blood and nerve supply, such as cartilages, tendons, and scleras. Calcium deposition may follow. The skin may be pigmented in a butterfly pattern on the nose and cheeks. The cerumen may be brownish-black, and the suderiferous glands may excrete homogentisic acid in sufficient quantities to cause the axilla to turn dark.[8] The arthritis most commonly involves the spine, shoulders, knees, and hips.[3] Urinary and prostatic ochronotic calculi have been encountered.[9] An increased incidence of cardiovalvular lesions, particularly aortic stenosis, has been described.[10] Other con-

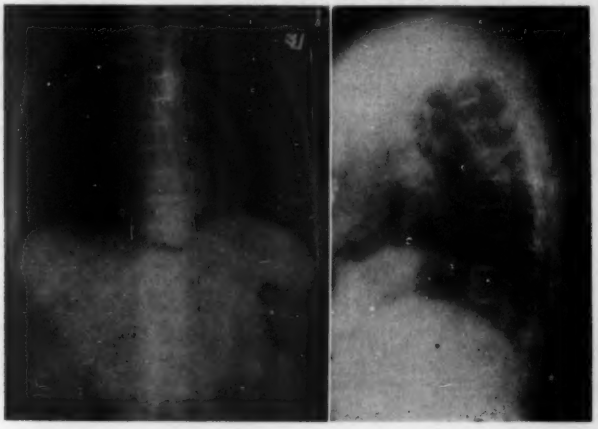

Fig. 3.—X-rays of lumbar and thoracic spine demonstrate thinned and calcified intervertebral discs.

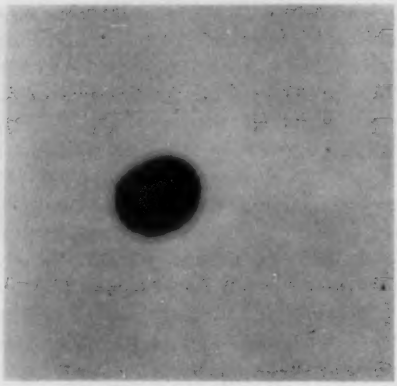

Fig. 4.—Positive Fishberg test. A drop of alkalinized urine causes exposed photographic paper to turn dark within seconds at the area of contact.

junctival findings have been described as brown pigment deposited within tiny cystic lymphatic dilatations in a circular manner, forming signet rings and hemispheric figures.[11] The skin of the eyelids may also be pigmented.[6]

Summary

Ochronosis is a rare disease resulting from defective phenylalanine metabolism with excretion of homogentisic acid in the urine. It is characterized by (1) pigmentation of the ears and sclera, (2) urine that darkens on exposure to air, and (3) osteoarthritis. Eye findings are almost always present and are characterized by slate-gray pigmentations of the sclera near the temporal and nasal limbus, deposits of brown droplets in the conjunctiva, and similar droplets in the cornea at the level of Bowman's membrane. X-ray findings, particularly calcification and thinning of the intervertebral discs, are often characteristic of the disease. Important laboratory tests include darkening of the urine on standing or after addition of 10% sodium hydroxide and rapid darkening of exposed photographic paper by a drop of alkalinized urine.

1363 Butler Ave. (2).

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Treatment of Herpes Zoster Ophthalmicus with Corticotropin and Corticosteroids

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This paper presents further observations on the treatment of herpes zoster ophthalmicus with corticotropin and corticosteroids. In a previous paper Scheie and Alper [1] reported the results obtained by the use of corticotropin and cortisone in 11 patients, 10 of whom showed complete recovery. The present report summarizes the treatment and course of 25 more patients with herpes zoster ophthalmicus who have been treated with hormones given systemically. All of the patients had typical cutaneous changes accompanied by ocular involvement and severe pain. Further experience has strengthened our initial conclusion that hormones exert a favorable influence when used therapeutically for herpes zoster ophthalmicus. Relief of pain usually is achieved in one or two days, and the ocular lesions show prompt improvement. The course of the skin lesions seems shortened.

Several reports on the use of corticotropin and corticosteroids have appeared since the review of the literature in our previous paper. Doenges [2] reported 15 cases of cutaneous and 1 of ophthalmic herpes zoster. These patients were treated with systemic cortisone. He felt that in the cutaneous form there was no definite advantage in hormonal treatment except perhaps in the prevention of scar formation. He thought cortisone was of real value in the treatment of ocular herpes zoster. Hogan, Thygeson, and Kimura [3] reported two patients treated with topical cortisone and two with topical hydrocortisone. The first two became worse on therapy, and the second two showed no noticeable improvement. Marshall [4] used topical hydrocortisone to treat three patients with herpes zoster, one of whom had uveitis and episcleritis. He concluded that marked relief of pain occurred and that the skin lesions regressed more rapidly than was usually expected. Relief of pain occurred within 24 to 96 hours of starting treatment. Appelman [5] reported four patients successfully treated by the use of corticotropin given intramuscularly or intravenously. One of the patients had herpes zoster ophthalmicus. He concluded that corticotropin shortened the acute phase, diminished pain, and helped to avoid complications. Benedict [6] reported one patient with herpes zoster ophthalmicus and keratitis treated with topical hydrocortisone and another with iritis and extraocular muscle involvement treated with topical and oral cortisone and intramuscular vitamin B_{12}. He felt that the course of the disease was favorably altered.

Carter [7] reported 15 patients with herpes zoster ophthalmicus treated by prednisone. All patients had conjunctivitis. Six had keratitis and associated iridocyclitis. He hesitated to draw conclusions regarding the efficacy of treatment from the small series, but he did believe that the course of the skin lesions was less severe. Epstein and Allington [8] reviewed treatment of 251 patients with herpes zoster. Eleven of these received corticosteroids. In their opinion, no real alteration in the course of the disease resulted with any of the current methods of treatment. Drs. Elliott and Sulzberger, in discussing the paper by Epstein and

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Allington, advocated a combination of cyanocobalamin and corticotropin. Sheard and Felder[9] reported one case of herpes zoster involving the geniculate ganglion which subsided promptly and without sequelae on treatment with corticotropin.

Classical descriptions of the ocular complications of herpes zoster are frequently misleading because the reader gains the impression that each occurs in an isolated manner, for example, keratitis. However, in our experience herpes zoster ophthalmicus usually produces a diffuse ocular involvement, just as might be anticipated from the confluent nature of the skin disturbance. The eyes usually show ciliary injection with an iridocyclitis which may vary in severity. Iridocyclitis is frequently associated with edema of the cornea and folds in Descemet's membrane. Scleritis may occur. Secondary glaucoma may occur and be very intractable. Any part of the picture may predominate, but secondary glaucoma and corneal opacity have usually been the most devastating complications. Numerous other complications may occur including optic neuritis, extraocular muscle pareses, and retinal detachment. Iridocyclitis and corneal infiltrates may recur or progress for months or even years after the acute process. The infiltrates may be accompanied by corneal ulceration but more frequently begin as superficial corneal infiltrates with the silken-sheen appearance characteristic of some virus diseases of the cornea. They may regress and disappear or advance toward the center of the cornea with an actively infiltrated slightly undermined border (Figure).

The 25 patients here reported all showed involvement of the eye. All of them had iridocyclitis or uveitis (Table 1). Twelve of them had corneal edema manifest by clouding and folds in Descemet's membrane. Three patients showed corneal infiltrates at the level of Bowman's membrane characteristic of virus infection, and two showed superficial corneal erosion, in addition to signs of intraocular involvement.

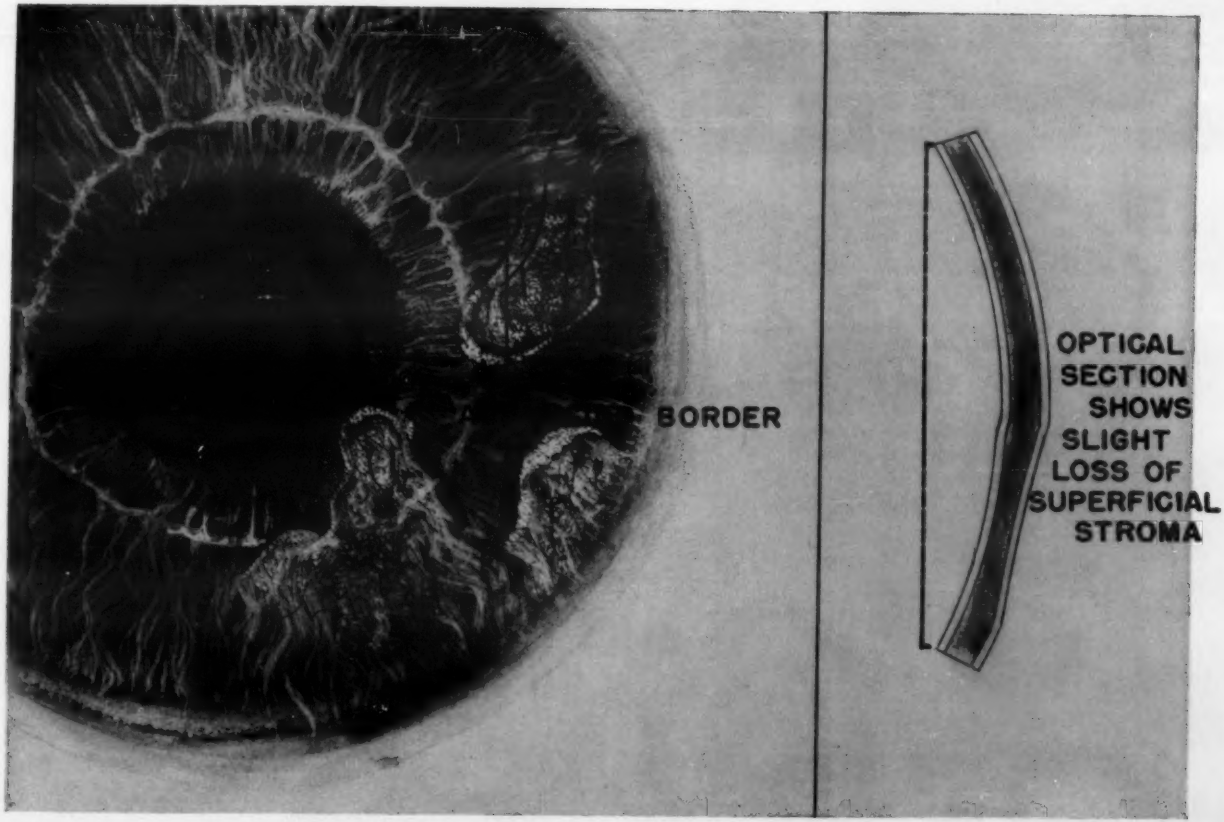
TABLE 1.—*Types of Ocular Involvement in Twenty-Five Patients with Herpes Zoster Ophthalmicus*

Iridocyclitis	8
Iridocyclitis with corneal edema	8
Uveitis with corneal edema	4
Iridocyclitis with herpetic corneal infiltrates	2
Iridocyclitis with superficial corneal erosion	1
Uveitis	1
Uveitis with herpetic corneal infiltrates	1
	25
Secondary glaucoma	5

All patients in this series were given topical atropine and hydrocortisone-neomycin ointments in addition to systemic therapy (Table 2). The skin lesions were treated with topical hydrocortisone to the stage of crust formation. Those whose skin lesions were severe enough to make secondary infection a definite risk were given prophylactic antibiotics systemically. All patients received systemic corticotropin or corticosteroids alone or in combination. In most cases the initial dose of corticotropin was 40 units intravenously. When improvement had occurred with intravenous therapy, intramuscular corticotropin was substituted; a few days before stopping parenteral therapy oral corticosteroids were started. The patients were discharged to outpatient follow-up a few days later. In nearly all patients oral hormones were continued for several weeks after complete clearing of the aqueous and resolution of the corneal lesions.

In most patients definite improvement was apparent within 24-48 hours after beginning therapy. Pain responded promptly, and analgesics were rarely needed after the second day of hospitalization. In the same period inflammation began to regress. The ciliary flush almost always diminished after the first day of treatment, and the aqueous began to clear by the second to fourth day.

Five of this group had secondary glaucoma at the time of admission. In four of them the intraocular pressure fell to normal on 48 hours of hormone therapy. The fifth had severe uveitis and intraocular pressure of 60 mm. Hg. In addition to systemic hormone therapy, acetazolamide was given



Lesions of chronic keratitis following herpes zoster ophthalmicus.

TABLE 2.—*Summary of Findings and Therapy on Twenty-Five Patients with Herpes Zoster Ophthalmicus*

No.	Age, Yr.	Date of Onset	Eye	Predominant Eye Manifestation	Systemic Hormonal Therapy: Substance	Daily Dose	Route	Duration, Days	Course of Ocular Lesions	Sequelae
1	56	4/30/54	Right	Iridocyclitis	Acthar	40 U.	I M.	9	Pain subsided in 2 days; iridocyclitis cleared in 12 days; topical steroid therapy continued to 1 mo.	None
2	34	6/ 5/54	Left	Iridocyclitis, with corneal edema	ACTH	20 U.	I. V.	3	Subsided in 4 days	None
					Acthar	40 U.	I. M.	1		
3	37	1/24/55	Right	Uveitis, severe; many K. P.; marked edema & thickening	ACTH	20 U.	I. V.	3	Initial attack subsided; recurrence in 48 days with tension of 46; suppressed with systemic hormones; two further recurrences suppressed with topical therapy	Permanent corneal edema. Recurrent iridocyclitis. V. A. 6/24
					Acthar	40 U.	I. M.	3		
					Cortisone	50 Mg.	Oral	25		
4	64	2/15/55	Left	Iridocyclitis; punctate staining of cornea	ACTH	20 U.	I. V.	3	Subsided in 18 days	None
					Acthar	40 U.	I. M.	9		
					Cortisone	50 Mg.	Oral	28		
5	55	3/ 3/55	Left	Iridocyclitis; corneal edema	ACTH	40 U.	I. V.	2	Little initial response; subsided after 5th day on increased dose	None
					Acthar	20 U.	I. M.	2		
					Acthar	40 U.	I. M.	7		
					Cortisone	50 Mg.	Oral	26		
6	66	5/10/55	Left	Iridocyclitis, marked corneal edema with folds in Descemet's membrane	ACTH	40 U.	I. V.	2	Subsided in 2½ wk.	Iridoplegia
					Acthar	40 U.	I. M.	5		
					Cortisone	50 Mg.	Oral	30		
7	57	8/18/55	Left	Iridocyclitis, corneal edema	ACTH	40 U.	I. V.	3	Subsided in 3 wk.	None
					Acthar	80 U.	I. M.	7		
					Prednisone	20 Mg.	Oral	13		
8	7	10/11/55	Left	Iridocyclitis, corneal edema	Acthar	40 U.	I. M.	13	Subsided in 2 wk.	None
					Acthar	20 U.	I. M.	1		
					Acthar	20 U.	I. M.	1		
9	62	3/ 5/56	Right	Iridocyclitis, corneal edema	Acthar	40 U.	I. M.	7	Subsided in 14 days	None
					Acthar	Tapered	I. M.	7		
					Prednisone	10 Mg.	Oral	21		
10	8	5/ 8/56	Left	Uveitis	Acthar	40 U.	I. M.	10	Subsided in 1 mo., one mild recurrence of iridocyclitis at 6 mo., suppressed with topical treatment	None
					Acthar	20 U.	I. M.	3		
					Acthar	10 U.	I. M.	2		
					Acthar	5 U.	I. M.	1		
					Cortisone	100 Mg.	Oral	15		
11	55	7/ 1/56	Left	Iridocyclitis, secondary glaucoma	ACTH	40 U.	I. V.	5	Tension normal in 1 day; gradual clearing in 13 days; one mild recurrence suppressed with oral cortisone	Corneal scar. visual acuity 6/12
					Acthar	40 U.	I. M.	6		
					Prednisolone	20 Mg.	Oral	7		

TABLE 2.—*Summary of Findings and Therapy on Twenty-Five Patients with Herpes Zoster Ophthalmicus*—Continued

No.	Age, Yr.	Date of Onset	Eye	Predominant Eye Manifestation	Systemic Hormonal Therapy: Substance	Daily Dose	Route	Duration, Days	Course of Ocular Lesions	Sequelae
12	72	10/30/56	Left	Iridocyclitis	ACTH	20 U.	I. V.	3	Subsided gradually	Corneal scar, visual acuity 6/9
					Prednisone	20 Mg.	Oral	12		
13	76	11/30/56	Right	Iridocyclitis, corneal edema	Acthar	80 U.	I. M.	3	Subsided in 7 days	None
					Acthar	20 U.	I. M.	4		
14	69	12/ 1/56	Left	Iridocyclitis, secondary glaucoma	Acthar	40 U.	I. M.	5	Tension normal in 2 days; one recurrence with episcleritis suppressed with oral prednisone	None
					Prednisone	20 Mg.	Oral	15		
15	60	2/20/57	Left	Uveitis, severe; many K. P.; corneal edema; secondary glaucoma (T-60 mm. Schiotz)	ACTH	40 U.	I. V.	3	Controlled promptly by hormonal therapy; tension normal with addition of acetazolamide; repeated recurrences over 2 yr.; controlled by oral & topical corticosteroid therapy	Repeated recurrences, iridoplegia
					Acthar	40 U.	I. M.	5		
					Acthar	60 U.	I. M.	2		
					Prednisone	20 Mg.	Oral	16		
16	57	4/ 1/57	Right	Iridocyclitis	ACTH	40 U.	I. V.	3	Subsided in 12 days	None
					Acthar	80 U.	I. M.	4		
					Prednisolone	20 Mg.	Oral	3		
17	49	4/11/57	Right	Iridocyclitis, herpetic corneal infiltrates (developed herpes while taking prednisone 15 mg. daily, mycosis fungoides)	Prednisone	20 Mg.	Oral	43	Prednisone increased to 20 mg.; subsided promptly; died of leukemia 43 days after onset of herpes	Eye quiet at death
18	65	6/17/57	Right	Iridocyclitis, corneal edema	ACTH	20 U.	I. V.	3	Subsided in 5 wk.	Optic atrophy noted at 6 wk.
					Acthar	40 U.	I. M.	4		
					Prednisolone	10 Mg.	Oral	39		
19	56	7/ 9/57	Right	Iridocyclitis	ACTH	20 U.	I. V.	4	Subsided in 3 wk.	None
					Acthar	40 U.	I. M.	2		
					Prednisolone	10 Mg.	Oral	8		
20	66	2/13/58	Right	Uveitis; many K. P.; corneal edema; secondary glaucoma (tension-36 mm. Hg)	ACTH	40 U.	I. V.	1	Tension normal in 1 day, subsided in 18 days	None
					ACTH	20 U.	I. V.	4		
					Acthar	40 U.	I. M.	1		
21	27	3/23/58	Left	Iridocyclitis	ACTH	40 U.	I. V.	4	Subsided in 5 days	None
					Acthar	40 U.	I. M.	2		
22	68	7/ 2/58	Left	Uveitis, herpetic corneal infiltrates	Acthar	40 U.	I. M.	1	Intense pain subsided on increased dose of ACTH intravenously; on change to prednisolone pain recurred; change to methyl prednisolone with dramatic relief; 1st attack subsided; recurrent iridocyclitis; controlled on each occasion with methyl prednisolone	Recurrent iridocyclitis
					ACTH	60 U.	I. V.	1		
					ACTH	40 U.	I. V.	2		
					ACTH	25 U.	I. V.	7		
					Prednisolone	16 Mg.	Oral	4		
					Methyl prednisolone	16 Mg.	Oral	21		

23	68	8/10/58	Right	Iridocyclitis, herpetic corneal infiltrates	Acthar	40 U.	I. M.	4	Subsided in 6 days	None
					Prednisolone	20 Mg.	Oral	8		
24	51	11/ 8/58	Left	Iridocyclitis, secondary glaucoma	ACTH	40 U.	I. V.	4	Subsided in 6 days, recurrences with secondary glaucoma suppressed with methyl prednisolone	Recurrent iridocyclitis
					Acthar	40 U.	I. M.	4		
					Methyl prednisolone	16 Mg.	Oral	15		
25	67	12/ 1/58	Left	Iridocyclitis, severe; corneal edema	ACTH	40 U.	I. V.	6	Little change on initial dose; improved on increased dose, then subsided satisfactorily	None
					ACTH	60 U.	I. V.	2		
					ACTH	40 U.	I. V.	3		
					Methyl prednisolone	16 Mg.	Oral	60		

for four days. The pressure was normal by the fourth day. Acetazolamide was discontinued, and intraocular pressure remained normal for the rest of the recovery period.

The courses of seven of the patients indicate that the hormones have little if any effect on the virus which causes herpes zoster but that they act in a protective manner during the acute period of involvement. One of the patients developed herpes zoster ophthalmicus accompanied by iridocyclitis and corneal infiltrates, while receiving oral corticosteroid therapy for leukemia. His ocular inflammation quieted after the dose of steroid was increased. Even after control of the initial attack, the manifestations of herpes zoster ophthalmicus can recur. This is especially true of keratitis and iritis, but the recurrences can usually be readily controlled by hormonal therapy. Six patients in this series suffered recurrences of iridocyclitis after the initial episode had subsided and treatment had been stopped. Recurrences usually responded to resumption of corticosteroid therapy as readily as the initial attacks.

Two patients in the group have had serious sequelae—one a permanent corneal edema resulting from repeated attacks of severe uveitis with presumably damage to the corneal endothelium. The final visual acuity was 6/24. Another suffered loss of vision from optic atrophy. Two patients had corneal opacity with resulting visual acuities of 6/9 and 6/12. Two patients had permanent iridoplegia. Twenty-one patients suffered no visual impairment.

Comment

It is difficult to assess therapy in a disease like herpes zoster ophthalmicus, which may show spontaneous remission and whose severity is hard to quantitate. Stokes [10] said that paralyses result from about 50% of cases of cephalic herpes zoster. Gundersen [11] discussed a control group of 19 untreated cases of herpes zoster ophthalmicus. Eleven lost vision to 6/60 or less (58%). Two declined to 6/15 or less (11%). Six re-

tained normal vision (31%). In the series reported here normal vision was retained by 21 (84%). Two had severe visual loss (8%), and two had moderate visual loss but retained useful vision (8%).

Gundersen [11] reported 22 patients treated with convalescent blood. Twelve of these (55%) were favorably affected. In seven (32%) the effect was doubtful, and in three (13%) there was no apparent effect. For a time convalescent blood therapy was used in our clinic with similar favorable results.[1] However, the difficulty of procuring donors and the hazard of reactions with frequent transfusions led to the use of other therapeutic approaches as they became available. In our experience systemic treatment with corticotropin and corticosteroids has been the only successful alternate to convalescent blood therapy. On the dermatology service of the Hospital of the University of Pennsylvania corticotropin and corticosteroids are used in severe cases of herpes zoster, especially for those patients who have severe pain or deep skin lesions. Most such patients receive oral triamcinolone, but those with gangrenous or very widespread painful lesions are given intravenous corticotropin. Dr. Walter Shelley, who saw a number of our patients in dermatologic consultation, has stated that in the treatment of cutaneous lesions corticotropin and corticosteroids give better results than other forms of therapy.[12]

Conclusions

The clinical course of 36 patients with herpes zoster ophthalmicus, including 11 patients previously reported,[1] indicates, in general, a favorable response to systemic therapy with corticotropin and corticosteroids. It is to be emphasized that those patients who do not improve initially do respond when the dose of corticotropin is increased to 60 to 80 units daily. Recurrences of iridocyclitis seem to improve as rapidly with hormone treatment as does the initial attack. None of the patients in our series have shown any exacerbation of the disease which might be attributable to hormone treatment.

Summary

Thirty-six patients with herpes zoster ophthalmicus treated with systemic corticotropin and corticosteroids have now been presented. Significant visual loss has occurred in only two eyes.

The commonest complications of herpes zoster ophthalmicus are iridocyclitis and corneal opacity.

Recurrences of iridocyclitis and keratitis after the initial attack subsides can be suppressed readily with corticosteroids.

No ill effect on the eye disease has been seen in our patients treated with corticotropin and corticosteroids.

Results of treatment seem to indicate that systemic corticotropin and corticosteroids exert a very favorable effect on herpes zoster ophthalmicus.

313 S. 17th St. (3).

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The Range of Normal for Visual Fields by Flicker Fusion

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Flicker fusion frequency may be measured in terms of either increasing or decreasing rates at which successive visual stimuli are presented to the subject. In this work, a decreasing rate was used and flicker fusion frequency is defined as the rate at which the subject noted a change from a continuous to an interrupted sensation. It is expressed in cycles per second.

Although flicker fusion was known to be a sensitive method of examining the retina and optic pathways, it was not until 1933 that Phillips[11] demonstrated its utility for examination of visual fields of several neurological patients and three normal subjects. His work was carried on and extended by Riddell,[12] working with the same equipment but with modified technique. He tested 15 normal subjects at 16 points in the visual field.

Hylkema[3,4] tested 33 light-adapted normal subjects at four points on the horizontal meridian, reaching 25 degrees nasally and 40 degrees temporally, employing a 5 degree test object. Working with fewer subjects, he also made more extensive tests with other sizes of test objects at more points on the horizontal and vertical meridians.

A different approach was used by Weekers and Roussel.[14] They took advantage of the known effect of the size of test object, i. e., the larger the test object, within limits, the higher the flicker fusion frequency, to control the rate at which flicker was perceived in different areas of the field. They adjusted the size of the test objects to the area tested so that the flicker fusion frequency in all the 26 areas which they tested, regardless of the age in the 49 normal subjects with which they worked, fell between 43 and 30 cps for the undilated eye. Having established their normal values by this method, they extended their studies by comparing the flicker fusion fields with those on the regular tangent screen in patients with retinal detachment, opacities of the media, tobacco amblyopia, glaucoma, arteriosclerosis, and central nervous system lesions. Dark-adaptation of 10-15 minutes was used throughout their experiments.

Miles,[9,10] in 1949, introduced the stroboscopic light for doing flicker fusion fields. He charted the fields of the light-adapted eye both on the tangent screen and the perimeter. In addition to normal subjects, he studied amblyopia ex anopsia, glaucoma, and neuro-ophthalmic lesions.

Havener and Henderson, with use of Miles' technique, compared the results of flicker fusion fields with those of standard methods of field examination, including color fields, in 90 patients with a variety of eye diseases and central nervous system and circulatory disorders.

In spite of this work, the range of normal has not been well-delineated. It seemed to us as though this would need to be done before clinical fields could be properly understood. Therefore, the present study was undertaken to establish the range of normal critical flicker fusion frequencies for three different sizes of test object, under conditions which could be easily duplicated in a clinic or office.

Submitted for publication March 4, 1959.

This study was supported by the Connecticut Lions Eye Research Foundation.

From the Department of Surgery, Section of Ophthalmology, Grace-New Haven Hospital, Yale University School of Medicine.

Method

Subjects.—Fifty-nine normal subjects (102 eyes) were chosen from hospital personnel, both men and women, from 18 to 65 years of age. Refractive errors which could be corrected to 20/20 were acceptable, and subjects were tested wearing their glasses. All had normal fields as tested with a 2 mm. white test object at 1 m. on a black tangent screen under 8 ft-c. illumination. Each subject was tested three times, first with a 1½ degree test object, at another time with a ½ degree test object, and on a third occasion with a 2 degree test object.

So many things have been said to alter flicker fusion that we drew up the history sheet shown in Figure 1. Almost all authors on the subject mention the effect of age and pupillary size. Krasno and Ivy [5] and Weekers and Roussel [14] mention the effect of cardiovascular disease and hypertension; Ivy, Krasno, and Roback [6] studied the effects of many commonly used drugs—barbiturates, antihistaminics, acetophenetidin, and caffeine which depress and dexedrine and benzadrine which increase flicker fusion frequency, and Marty and Hardy [7] used flicker fusion to prognosticate toxemias of pregnancy and the prognosis thereof.

HISTORY SHEET

NAME HOSPITAL NUMBER

AGE SEX RACE OCCUPATION

GENERAL HEALTH (heart or lung disease, etc.)

DRUGS

ALCOHOL

TOBACCO

BLOOD PRESSURE

OPHTHALMIC HISTORY

EXAMINATION OF EYES

VISION

PUPIL SIZE

FUNDI

OPACITIES

Fig. 1.—Sample history sheet used in screening normal subjects.

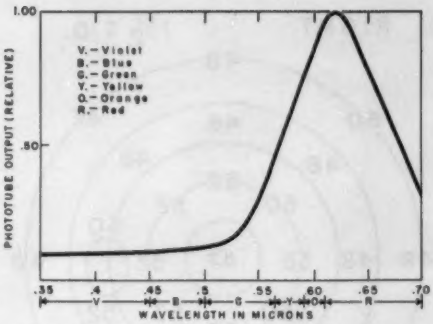

Fig. 2.—Spectrum of the Strobotac bulb in microns.

Apparatus.—The Strobotac described by Miles was used in the current experiments. The light produced is orange in color and has a wave length of 0.625μ (Fig. 2). The duration of the flash with the switch on "low" lasts approximately 40μsec. The bulb has a peak of 0.02 to 0.03 megacandle power.

The Strobotac was modified as follows: The glass and bulb were removed from the "bull's eye" on the front of the housing. A cord was plugged into the socket and led through a semirigid plastic tube to a rectangular gray housing in which the bulb was mounted. This constituted the "wand" and was painted gray. A removable side-panel allowed insertion of different sizes of test object, ½, 1½, and 2 degrees. A translucent piece of plastic was used to obscure the filament.

A gray tangent screen at 1 m. served as the surround, with an illumination of 18 ft-c., measured with a Weston Illumination Measure. This is rather more light than one might ordinarily use, but we knew of similar work being done at 8 ft-c. and felt we would supply more new information by picking a different level of illumination.

Technique.—The history was taken, and pupils were measured with the subject gazing at the central fixation spot on the screen. The Strobotac was warmed up for 10 minutes before use. Before the first test on any subject, the procedure was explained and demonstrated.

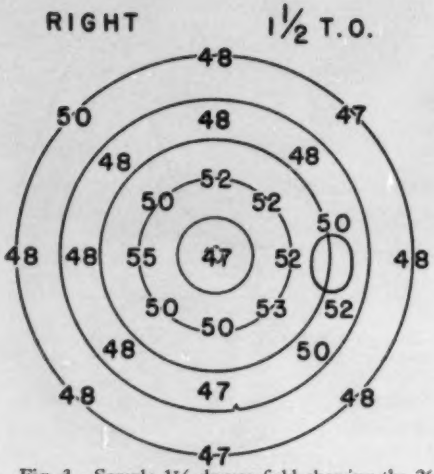

Fig. 3.—Sample 1½ degree field showing the 26 areas tested; readings in cycles per second.

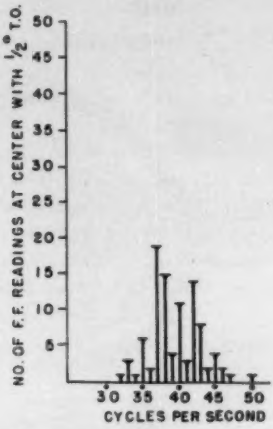

Fig. 4.—Range and distribution curve of flicker fusion frequencies in the center of the field with a ½ degree test object.

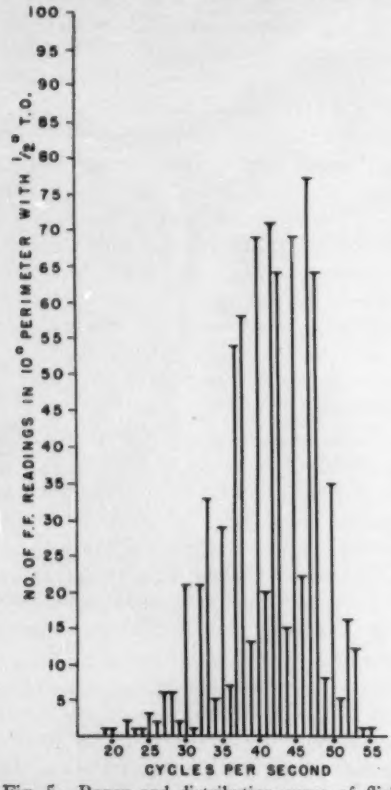

Fig. 5.—Range and distribution curve of flicker fusion frequencies in the 10 degree perimeter with a ½ degree test object.

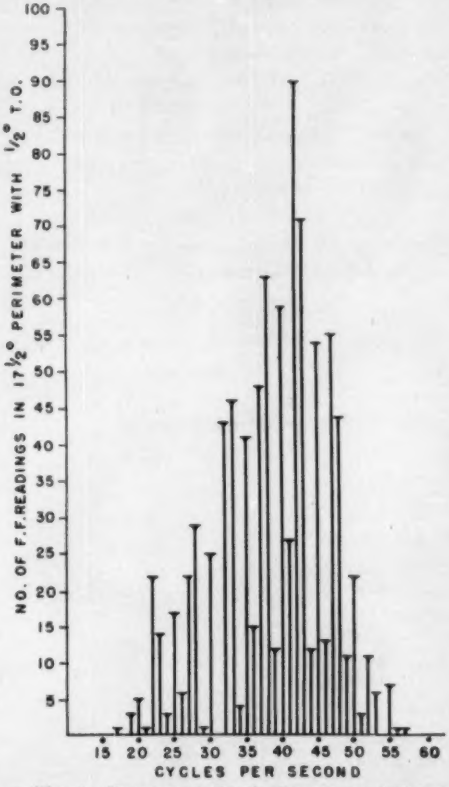

Fig. 6.—Range and distribution curve of flicker fusion frequencies in the 17½ degree perimeter with a ½ degree test object.

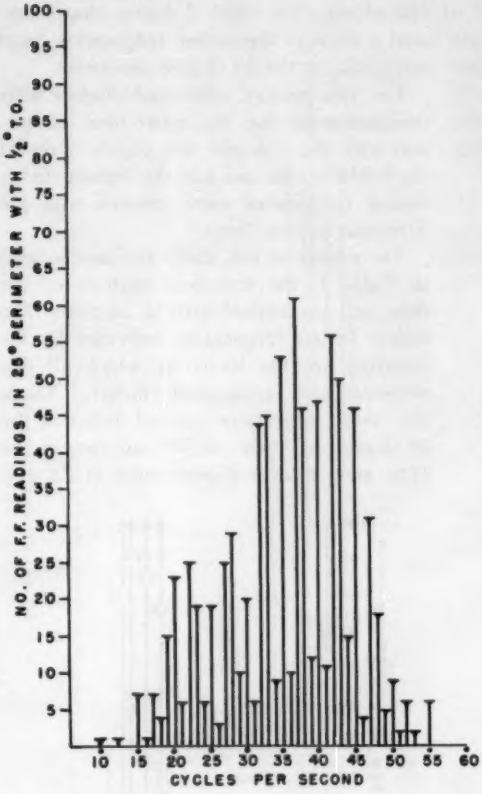

Fig. 7.—Range and distribution curve of flicker fusion frequencies in the 25 degree perimeter with a ½ degree test object.

Starting with an apparently steady light, the rate of flicker was rapidly reduced until the subject signified that flicker was perceived.

Twenty-six areas were tested on each eye, one central, eight in the 10 and 25 degree perimeters, and nine in the 17½ degree perimeter.

The speed of flicker was read on the Strobotac as revolutions per minute, converted to cycles per second, and charted as shown in Figure 3.

A cream-colored metal shield clipped on to a spectacle frame, so that light was not excluded, was used to cover the eye not being tested.

Subjects were seated behind a vertically adjustable table which held a chin and forehead rest.

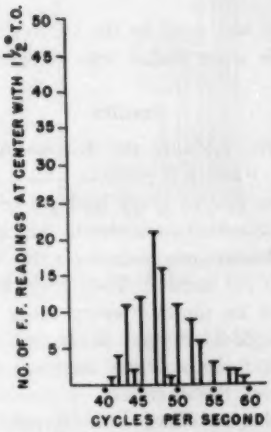

Fig. 8.—Range and distribution curve of flicker fusion frequencies at the center with a 1½ degree test object.

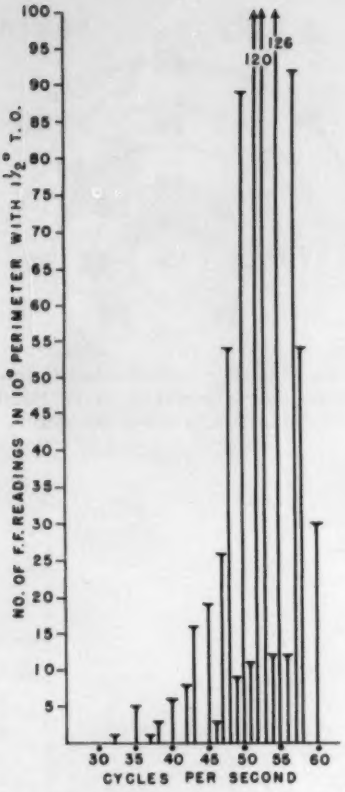

Fig. 9.—Range and distribution curve of flicker fusion frequencies in the 10 degree perimeter with a 1½ degree test object.

A key was used by the subject to tap on the table when flicker was recognized.

Results

Figures 4-15 are the distribution curves for the three test objects. Low numbers on either side of every multiple of five are mathematical artifacts due to the conversion of revolutions per minute on the Strobotac to cycles per second. They could have been observed by plotting every other number, i. e., 20-22-24-26 and so on, so it is not felt that these artifacts interfere with the validity of the curves.

Bell-shaped curves are formed by the data taken with the ½ and 1½ degree test objects and the center with the 2 degree test object. The other 2 degree charts present a skew to the higher frequencies, most noticeable in the 10 degree perimeter.

For this reason, additional studies were undertaken to find the upper limit of normal with the 2 degree test object. Five of the subjects who had had the highest flicker fusion frequencies were retested with the Strobotac set on "high."

The results of this study are incorporated in Table 1, the statistical analysis of the data, and are marked with an asterisk. The flicker fusion frequencies indicated by the asterisks are the levels by which all five subjects had recognized flicker. Above this, three subjects recognized flicker in the 10 degree perimeter at 70 and two in the 17½ and 25 degree perimeters at 78 cps.

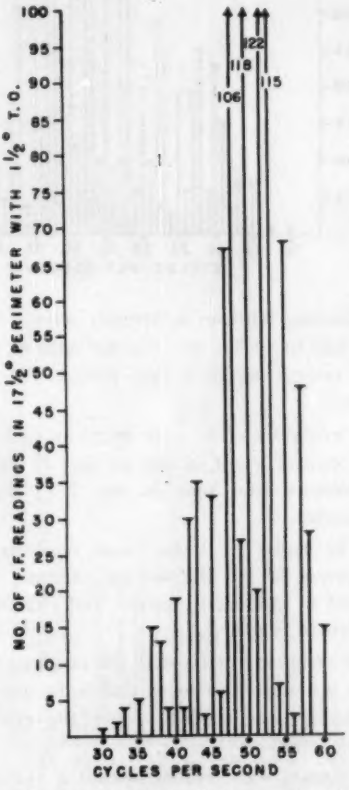

Fig. 10.—Range and distribution curve of flicker fusion frequencies in the 17½ degree perimeter with a 1½ degree test object.

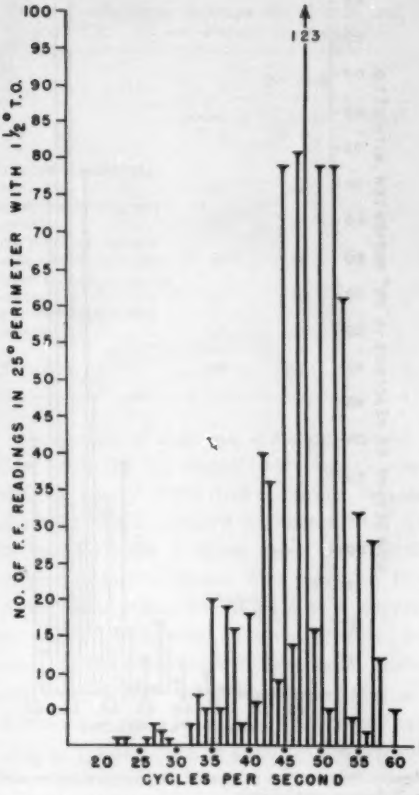

Fig. 11.—Range and distribution curve of flicker fusion frequencies in the 25 degree perimeter with a 1½ degree test object.

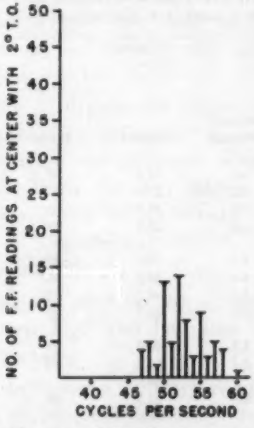

Fig. 12.—Range and distribution curve of flicker fusion frequencies at the center with a 2 degree test object.

These figures suggest that the mean, standard deviation, and median would all be increased, with the mean and median coming closer together so that a bell-shaped curve would be formed by the 2 degree data.

Table 1 shows that the low figures for the ½ and 1½ degree test objects show a progression downward from central vision to the 10 degree perimeter to the 17½ degree perimeter and finally to the 25 degree perimeter. With the 2 degree test object, even the low figures showed a slight rise in flicker fusion at the 10 degree perimeter, followed by a decline in flicker fusion frequency at the 17½ and 25 degree perimeters.

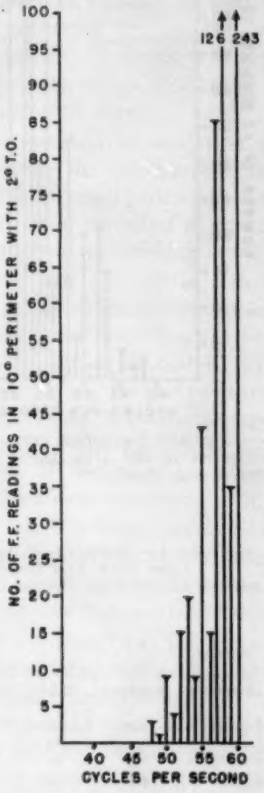

Fig. 13.—Range and distribution curve of flicker fusion frequencies in the 10 degree perimeter with a 2 degree test object.

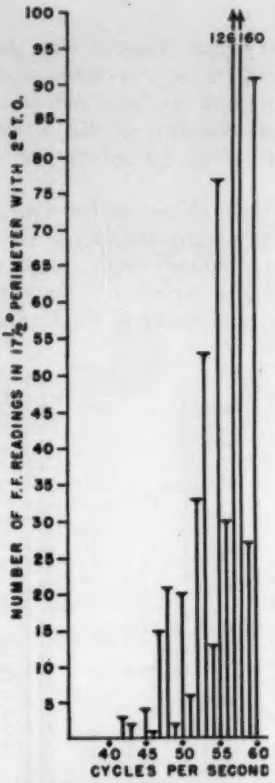

Fig. 14.—Range and distribution curve of flicker fusion frequencies in the 17½ degree perimeter with a 2 degree test object.

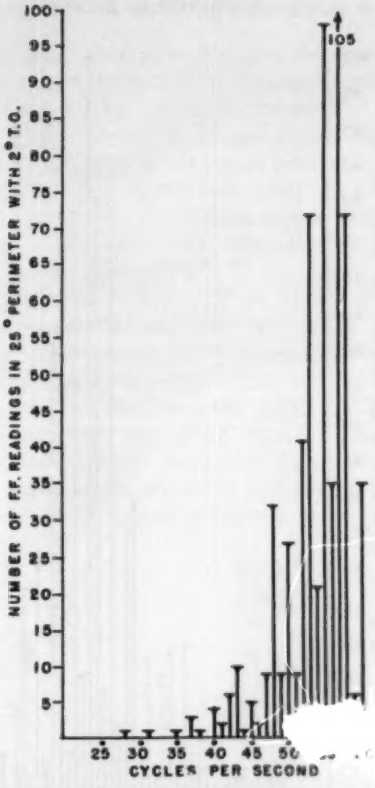

Fig. 15.—Range and distribution curve of flicker fusion frequencies in the 25 degree perimeter with a 2 degree test object.

TABLE 1.—*Summary of Statistical Analysis of Flicker Fusion Frequencies for Each Test Object and Each Position in Cycles per Second*

Object, Degrees	Position, Degrees Perimeter	No. Readings	High	Low	Mean	Standard Deviation	Median	Mode	Av. Difference Between High & Low for Each Eye
¾	Center	102	50	32	39.5	3.3	41.5	37	
	10	816	55	19	41.6	6.2	37.5	47	8.6
	17½	918	57	17	38.7	7.7	37.5	42	10.7
	25	816	55	10	35.5	8.8	33.0	37	11.3
1½	Center	102	59	41	48.1	4.0	50.5	47	
	10	816	60	32	52.2	4.4	46.5	55	5.4
	17½	918	60	30	49.7	5.2	45.5	52	6.9
	25	816	60	22	47.3	5.9	41.5	48	7.4
2	Center	76	60	47	52.4	3.1	54.0	52	
	10	608	60	48	57.9	2.5	54.5	60	2.2
			63 *				56.0		
	17½	684	60	42	55.9	3.6	51.5	58	4.5
			65 *				54.0		
	25	608	60	28	53.9	4.6	44.5	57	5.8
			65 *				47.5		

* These frequencies based on additional studies described in the text.

TABLE 2.—*Relations Between the Central and Peripheral Flicker Fusion Frequencies*

	No. Eyes		
	½ Degree T. O.	1½ Degree T. O.	2 Degree T. O.
All peripheral higher than central	9	20	31
Lowest peripheral equal to central	3	11	7
Some peripheral higher & some lower than central	47	40	25
Highest peripheral equal to central	6	11	9
All peripheral lower than central	37	20	4
Total eyes	102	102	76

This relation was not constant though. Even with the ½ degree test object, nine eyes, or nearly 10%, had a flicker fusion higher at the 25 degree perimeter than at the center, while in three more the lowest peripheral flicker fusion was equal to the central flicker fusion. With the 2 degree test object, there were 31 eyes, or 40%, in which all the peripheral flicker fusion readings were higher than the central and an additional 7 eyes in which the lowest peripheral reading was as high as the central flicker fusion. In order to show these patterns more clearly, we classified them in five categories, as shown in Table 2.

A comparison of the high and low flicker fusion frequencies for each eye of both eyes of one subject shows a wide variation in sensitivity to flicker.

With the ½ degree test object, there are 56 instances of a difference of more than 15 cps between the different areas in one perimeter. With the 1½ degree test object, there are only 16 such instances, while with the 2 degree test object, this only happened four times.

With all test objects, the greatest variation between high and low was in the 25 degree perimeter.

While there was a tendency for the higher readings to be located nasally and downward, as described by Hylkema,[4] it was not statistically significant.

TABLE 3.—*Comparison of Range of Flicker Fusion for Different Age Groups* *

Years	No. Eyes	Center	10 Degrees	17½ Degrees	25 Degrees
18-20	28	41-57	48-56	46-55	42-58
21-29	20	43-59	48-60	44-59	40-58
30-40	18	42-55	44-60	45-58	41-58
41-50	22	41-53	39-55	39-54	34-56
51 & over	14	42-50	43-55	38-50	33-49

* Based on averages of each eye with the 1½ degree test object expressed in cycles per second.

The difference between the central flicker fusion frequencies for the two eyes was greatest for the ½ degree test object, less for the 1½ degree test object, and least for the 2 degree test object.

Another method of analyzing our data was to average the 1½ degree flicker fusion frequencies for each perimeter of each eye. Using this data, the effect of age, pupillary size, and cigarette smoking were studied.

Effect of Age.—It will be seen from the figures in Table 3 that the highest values for flicker fusion were reached by persons between the ages of 20 and 40, while some of the lowest were, for this particular series, in the age group between the ages of 40 and 50 years. The number of eyes in the group over 50, however, is too small to be accepted without reservation. It is very possible that if a larger number of persons in the older age group were tested the range of flicker fusion frequencies would be found to extend lower than we found them.

Effect of Pupillary Size.—An attempt was made to tabulate the effect of pupillary size on flicker fusion frequency. While the tabulation seemed to support the recognized effect of pupillary opening on flicker fusion frequency, namely, that the largest pupils are expected to have a higher rate of flicker fusion, we have not included it because we realized that it correlated coincidentally with the effect of age on the pupillary opening. All subjects who had 5 mm. pupillary openings under test conditions were less than 30 years of age and, with one exception, those who had 3 mm. pupils were over 40 years of age.

TABLE 4.—*Range of Average Flicker Fusion Frequencies for Nonsmokers and Smokers*

	No. Eyes	Center	10 Degrees	17½ Degrees	25 Degrees
Nonsmokers	46	42-58	43-60	38-58	32-58
Smokers	56	41-59	43-60	41-59	37-58
One subject, 2 packs/ day, age 44	2	45-48	49-52	48-51	46-47

* Expressed in cycles per second with the 1½ degree test object at the center and in the 10 degree, 17 degree, and 25 degree perimeters.

Effect of Smoking.—Table 4 compares the average flicker fusion frequencies of smokers with those of nonsmokers, with use of data obtained with the 1½ degree test object. It will be seen that the range is comparable for the two groups. Referring back to Table 1, we find that this difference is not greater than the standard deviation for this size of test object.

Only one of our subjects smoked two packs a day. The findings on this subject are marked with an asterisk in Table 4 and compare favorably with others in her age group, shown in Table 3.

These figures seem to indicate that habitual cigarette smoking does not appreciably alter flicker fusion frequency.

Effect of Dominance.—Because of the relation already demonstrated between flicker fusion and amblyopia ex anopsia first by Lohmann (cited by Miles[9]), by Teraskeli,[13] by Mayer and Sherman,[8] and by Miles,[9] it occurred to us to investigate whether ocular dominance would show some particular pattern.

We tested 38 subjects for dominance by the pinhole method. No abnormally high central flicker fusion or a depressed peripheral flicker fusion in the nondominant eye, similar to the pattern in amblyopia ex anopsia, was found, nor was any other particular pattern associated with dominance. The patterns formed varied from one size of test object to the other for most subjects.

Comment

Two difficulties are peculiar to Strobotac. The first is an audible clicking in the bulb which varies with the speed of flicker. Some of our subjects were cognizant of this sound and its correlation with flicker. In discussion of this problem with Ginsberg, who is working with Carney Landis, the suggestion was made of "jamming" by means of another motor, such as an electric fan, in the room to obscure the Strobotac sound. However, we did not change the test conditions because a good deal of work had been done.

The second difficulty, for our particular project, was the limited overlap of the "high" and "low" settings on the machine, so that it was not possible to reduce the rate of flicker smoothly from over 60 to 40 or less. This would not be likely to interfere with fields done for clinical purposes.

We were not primarily interested in the effect of pupillary size, but it seemed as these data were being analyzed that to undertake work on this subject, it would be necessary to select subjects who were within a few years of each other in age or to have a large enough number of subjects in each age group that they could be classified on the basis of age as well as on the basis of pupillary size.

The finding of flicker fusion frequencies of 78 in the peripheral areas of two of our subjects is higher than others generally reported. However, Hylkema[3] reported a flicker fusion frequency of 82 in work with an episcotister, with a larger test object and greater illumination; Kennelly and Whiting,[15] in 1907, also working with an episcotister, estimated that the maximum frequency with a stationary target and a stationary eye should be in the neighborhood of 66 cps, and Erlick and Landis,[16] in 1952, showed that flicker fusion frequency was higher when measured with a Strobotac than with an episcotister. They attributed this to the difference in duration of the dark period in the flash cycle of the two methods. In our case, the relatively high level of general illumination may have been a contributing factor.

The lower limit of normal for a given size of test object is the more important limit clinically because pathology is always associated with a lowering of flicker fusion frequency. Table 1 records these for all three sizes of test object. In addition, low readings were not uncommon for the areas above or below the blind spot or both. This was probably the result of bringing the test object too close to the blind spot. It is probable that Weekers and Roussel [14] encountered similar difficulties because they used a 6 degree test object above and below the blind spot and smaller test objects elsewhere in that perimeter.

The technique used in the current study was fairly well standardized, and from an early phase of the work the important practice emerged of reducing flicker speed rapidly. Quick local adaptation of peripheral areas of the retina to flicker is well known, and not infrequently readings were recorded which were too low for the area tested. In our experience more reliable readings can be obtained for these doubtful areas by repeating the observations after an interval, usually after completion of the remainder of the field.

Our data show a wide range of individual variation for the ½ degree, less for the 1½ degree, and least for the 2 degree test object. The distribution of flicker fusion values for the center and each of the perimeters tested fell into a bell-shaped curve, except where the limitation of the apparatus forced the data to present a skew to the higher frequencies.

Comparing flicker fields with standard fields, we feel that the 2 mm. white test object fields can be done more rapidly and are easier to understand in that they create their own pattern. With flicker, a low reading in one area or in two separate areas usually casts doubt on the technique and was found to compatible with a normal field.

Over and above specific comparisons, though, there is the consideration that in one case the regular field may pick up a defect, while in another, the flicker fusion field may be the more revealing. This was the basis which Havener and Henderson used in assessing the usefulness of flicker fusion fields, and it is a compelling reason for doing flicker fusion fields in cases where fields are indicated, as well as standard fields.

In addition to this, there are the cases of opacities of the media in which form vision is so impaired that regular fields cannot be done, yet flicker fusion may produce very reliable fields.

Summary

We have worked out range and distribution curves for flicker fusion frequency with test objects of ½, 1½, and 2 degrees for the center, eight areas in the 10 degree perimeter, nine areas in the 17½ degree perimeter, and eight areas in the 25 degree perimeter, a total of 26 areas for each field, with 51 normal subjects and 102 eyes and with easily procurable apparatus under specified and easily reproducible conditions.

Our figures include the high, low, median, mean, standard deviation, mode, and average difference between high and low of flicker fusion frequencies expressed in cycles per second.

We have also sought to corroborate with our data known or suspected relationships between flicker fusion and age, pupillary opening, cigarette smoking, and ocular dominance.

Dr. Colin White, Head of the Biometries Department of the Yale University School of Medicine gave suggestions on the handling of data and on the figuring of standard deviation.

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Spontaneous Retinal Electrical Potentials

JERRY HART JACOBSON, M.D., and GIDON F. GESTRING, New York

Recent interest in psychopharmacology has led to extensive investigation of a number of types of drugs. The derivative of ergot known as D-lysergic diethylamide, or LSD-25, is one of the most thoroughly studied. This substance has been known to have pronounced effects upon the uterus, vagina, and bronchi and to cause mydriasis, tachycardia, rise in temperature, and other autonomic effects.[1] Hoffman,[2] in 1943, was the first to report psychic effects of the drug, after he had accidentally ingested a small quantity of it. These have been found to include mood changes, schizoid states, and, most important from the ophthalmological standpoint, visual hallucinations.

The doses required for production of hallucinations in man are extremely minute, as little as 0.5μg. to 1.0μg. per kilogram of body weight being effective.[3] Larger doses are required in schizophrenic patients.[4]

Recently Apter and Pfeiffer[5] reported their observation that upon administration of LSD-25 to cats, the animals behaved as though they were having visual hallucinations and that spontaneous electrical activity occurred in the eyeball of the cat when the drug was administered. The conclusion was drawn that, contrary to the opinion generally held that the visual disturbances of the drug were due solely to central nervous system effects, the peripheral action of the drug upon the retina must be considered as a participant in the production of the hallucination. Our study was undertaken in an attempt to determine the characteristics of this phenomenon.

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Mr. Richard Dowling gave technical assistance.

From the Division of Electrophysiology, Department of Research, New York Ear and Eye Infirmary and Albert Einstein College of Medicine.

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Methods

Forty-five adult cats were utilized in this study. The majority of the studies were performed by recording from the surface of the eyeball. In these experiments a chlorided silver electrode, 1 mm. in diameter, was sutured against the corneal surface about 1 mm. inside of the limbus. The animals were anesthetized with pentobarbital sodium, about 30 mg per kilogram, and artificially ventilated. The subclavian vein and femoral artery were cannulated, and remote control syringes were so arranged within a shielded chamber as to allow simultaneous systemic administration of drugs and recording of the blood pressure without disturbing the shield or the state of dark-adaptation. Bilateral recording was usually performed, and the outer canthus or the nose served as reference leads.

In another group of cats, the cornea, lens-iris diaphragm, and vitreous were removed. Micromanipulators were used to position and hold electrodes against the retinal surface.

Monkey and human excised retina was studied, with use of the technique which has been described elsewhere.[6]

A Grass polygraph unit was used for ink-writer recordings and a DuMont Type 333 dual-beam oscilloscope and Grass Kymograph camera for photographic records. Section of the optic nerve, when performed, was accomplished acutely by sharp traction on a silk suture which had been previously looped about the nerve at the chiasm. In chronic studies the nerve was sectioned at

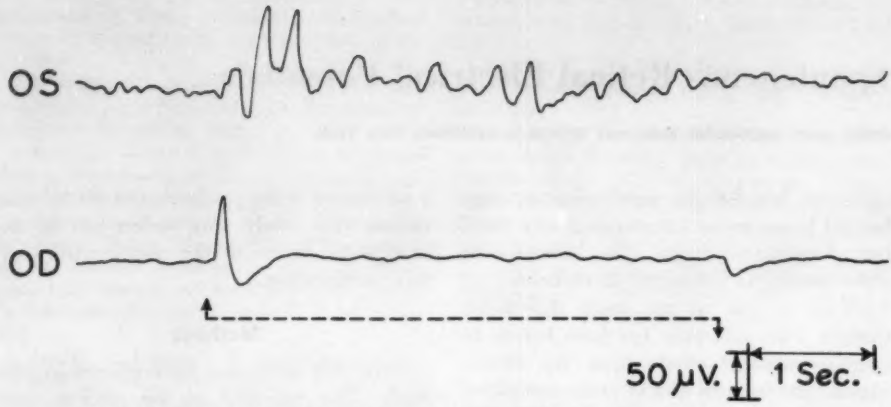

Fig. 1.—Effect of 100μg. of LSD-25 per kilogram on the ERG of the cat. "Spontaneous" potentials developing in cat eye after administration of LSD-25. Arrows indicate light stimuli. Tracing of right eye is after section of the optic nerve.

the chiasm after gentle retraction of the frontal lobes. In all "optic-nerve-sectioned animals" the central retinal circulation was kept intact and verified by ophthalmoscopic examination. All animals were adapted to total darkness for 20 minutes prior to recordings.

Results

In 40% of all animals given injections intravenously with LSD-25 at a dosage level of about 50μg. per kilogram of body weight, spontaneous potentials were recorded from the eyeball, sometimes triggered by light stimuli (Fig. 1).

Section of the optic nerve at the chiasm abolished these potentials. If the section was unilateral the spontaneous activity disappeared in the sectioned eye and persisted in the intact eye (Fig. 2).

Similar potentials can be shown to develop in animals which have suffered heavy blood loss or have had a large dose of barbiturate (Fig. 3).

Figure 4 shows a series of ERG's recorded from the surface of a cat eye. In the left column the topmost record is the response of a cat lightly anesthetized with pentobarbital. Additional doses of pentobarbital causes an increase in the *b*-wave amplitude until a maximum is attained (3d tracing). Added drug causes diminution of response until the original amplitude of response is reached (5th tracing). From

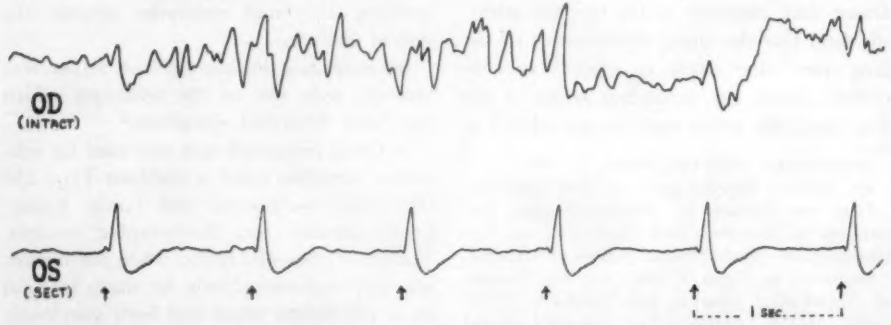

Fig. 2.—Recordings from both eyes of a deeply anesthetized cat with unilateral optic nerve section, showing "spontaneous" activity only in eye with intact nerve. Arrows indicate light stimulation. Normal ERG's in eye with sectioned nerve.

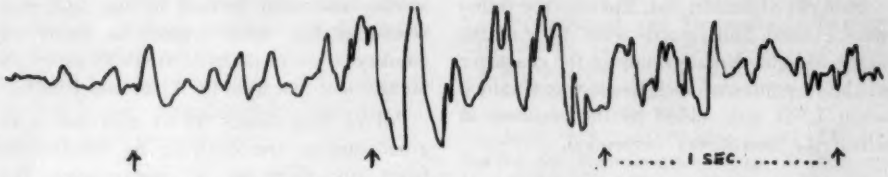

Fig. 3.—"Spontaneous" activity in eye of cat after heavy blood loss. Arrows indicate light stimulation.

this point on if one administers more barbiturate or LSD-25 or bleeds the animal, a sequence of changes as shown in the right hand column is induced. This reversal of sign is typical of deeply depressed animals. Most animals recover under artifical respiration and regain a normal response to light stimuli.

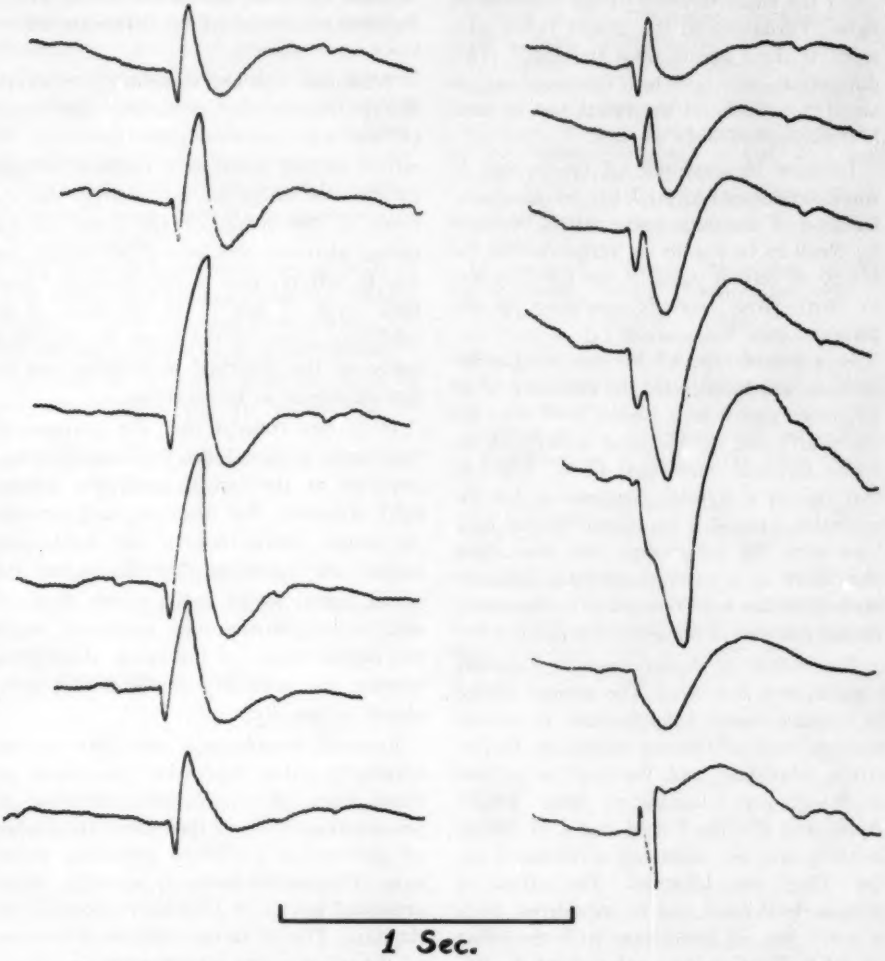

Fig. 4.—Sequential changes in ERG character in cat after serial doses of pentobarbital.

Samples of human, cat, and monkey retina were excised, and records were made of the tissue to light. No alteration in the character of the responses of such tissue was obtained when LSD was added to the medium in which the tissue was suspended.

Comment

The electrical activity of the retina may be modified by a variety of factors. A number of drugs, including barbiturates,[7,8] hexamethonium,[9] iodoacetate,[10] trichloroethylene,[11] ethyl alcohol,[12] and LSD-25, affect the characteristics of the response to light. Variations in the effects noted with some of these agents were striking.[13] This difference in character of response is noted[14] not only in the retina but in cerebral neurophysiology as well.

Increase in amplitude of the *a*- and *b*-wave components of the ERG due to administration of one toxic agent, trilene, thought by Noell to be due to an inhibition "of the ability of certain parts of the ERG system to shift from scotopic operation to the photopic one."[13]

In a recent report[9] we presented a hypothesis which projected the existence of an inhibitory center at a higher level than the retina affecting the electrical activity of the retina through centrifugal fibers. We feel that this is a possible explanation for the inhibition suggested by Noell. Clinical findings with the afterimage test also show that there is a marked cerebral influence upon what had been thought to be the purely retinal function of persistence of images.[15,16]

The matter of dosage must be carefully considered in this work. The amount needed to produce visual hallucinations in normal man, as reported, among others, by Mayer-Gross, McAdam, and Walker,[3] is as little as 0.5μg. per kilogram of body weight. Apter and Pfeiffer[5] used doses of 100μg. in their cats, or, assuming a normal 3 kg. cat, 33μg. per kilogram. The effect of pentobarbital must also be considered, since it too[17] has an interaction with the effect of LSD-25. Complexity is added to this already confused picture by the fact that blindness has been found to occur in monkeys[17] given doses of LSD-25 not much higher than that used by Apter and Pfeiffer.

All of this causes us to approach with great caution the drawing of conclusions from any given set of observations. We feel, for example, that the evidence of cats rubbing their eyes, peering into their cages, and grasping the air with their paws, as reported,[5] is rather tenuous evidence for the conclusion that "cats are capable of having hallucinations."[18] Similar effects can be seen upon the administration of drugs, for example, pentobarbital, before the animal loses consciousness.

With due caution, therefore, we should like to suggest the possibility that many of the electrophysiological variations in retinal activity noted as a result of administration of drugs are not entirely due directly to the action of the drugs on the retinal elements themselves but rather are due to effects upon a hypothetical "feedback" type of control, in the form of an inhibitory center in the brain. We feel that many of the observed phenomena can be best explained in this manner.

It is our concept that the purpose of this center is to stabilize the level of retinal impulses at the retinal level. An intense light stimulus, for example, will activate the center which in turn will inhibit the retinal activity level, thus decreasing the visual signal to an interpretable level. A weak signal, on the other hand, will reach the higher levels of the brain uninhibited because the inhibitory center is not stimulated to activity.

External interference with this delicate system by either depression (anesthesia or blood loss) or stimulation (electrical or pharmacological) will then cause an absence of appropriate inhibitory potentials at intense illumination levels or sporadic, uncoordinated bursts of inhibitory potentials in the dark. This is, in our opinion, the source of the spontaneous potentials observed.

A wide variety of drugs at certain dosage levels will probably produce effects similar to those described above. However, in all cases, spontaneous activity of this type is abolished by cephaloretinal interruption, such as optic nerve section.

Summary

Doses of D-lysergic diethylamide (LSD-25) (below 25μg. per kilogram) administered to cats systemically show no effect on the electrical potential of the eye.

Higher doses of LSD-25 (50μg.-100μg. per kilogram) sometimes produce spontaneous potential fluctuations in the intact eyeball of the cat.

Similar potentials can also be observed in animals which have suffered heavy blood loss or overdose of anesthesia (pentobarbital, sodium amobarbital [amytal], or ether).

Those potentials are abolished by section of the optic nerve, increase of anesthesia, or CNS stimulants.

The effect of large quantities of LSD-25 (over 200μg. per kilogram) on the ERG is identical to that observed upon administration of large quantities of pentobarbital.

LSD-25 has no effect upon the ERG of the excised retina of the human, cat, or monkey.

A hypothetical explanation of these phenomena is presented.

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Focal Senile Translucency of the Sclera

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The occurrence of discrete gray areas, often called plaques, in the sclera just in front of the medial and lateral recti is a common finding in old age. If these areas are excised together with a rim of normal sclera and held before a light, they show increased translucency. They are not pigmented and are not plaques in the usual sense of the word. Their gray color is due to enhanced visibility of the uveal pigment, but occasionally they do contain calcific plaques.

Since these focal spots are not known to have clinical significance, they have not attracted much attention and are poorly described in current textbooks and most reviews. The scanty literature up to 1945 was collected by Roper[1] in an article which incidentally presents the best clinical illustrations of the entity in the literature. That article emphasizes the association of the spots with age and points up the confusion which has resulted from misinterpretation of the entity as a form of scleromalacia perforans.

The histopathology of these scleral areas has been reported, in a total of only four cases: by Zavalia,[2] in 1937; Culler,[3] in 1939; Kyrieleis,[4] in 1939, and Pur,[5] in 1955, respectively. Zavalia's specimen, obtained by biopsy, was said to show signs of "hyaline degeneration and calcification" with loss of cellular elements. Culler's specimen was obtained at autopsy and is described as a ". . . seed-like mass which presented a marked tendency to break away from the surrounding sclera and could have been shelled out . . . composed of large masses of granular debris free from cellular structure and contained large masses of hyaline. There were no calcium deposits." This description is in striking contrast to the illustrations which accompany the article and which show clearly basophilic staining compatible with calcium and nothing which could be called hyaline. No special stains for calcium were done. Kyrieleis' specimen, obtained by enucleation for a choroidal melanoma, showed a calcific plaque and loss of cellularity in the adjacent sclera. Both this case and Culler's case were said to show thinning of the sclera, but this impression was apparently based on examination of fixed specimens after paraffin-embedding rather than on fresh tissue. Pur's specimen, obtained by biopsy, was described in a Czech journal not available to us, and no details of the pathologic findings are given in the abstracts which were available to us.

Our study was prompted by findings contrary to the previous pathologic descriptions and more particularly by a fortuitous finding that the calcific plaque in one case was composed almost entirely of gypsum (calcium sulfate).[6] Since this was the sole instance in which gypsum had been found in biologic tissue, it is important to establish whether or not gypsum is found in other cases with the same diagnosis.

For the present study observations were made on approximately 25 cases seen clinically and on 30 cases examined pathologically. The majority of the latter were obtained post mortem through the facilities of the Boston Eye Bank. In three cases crystallography of the calcific plaques was undertaken in a manner similar to that which had been used in the demonstration

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Howe Laboratory of Ophthalmology, Harvard University Medical School, and Massachusetts Eye and Ear Infirmary.

of the gypsum. In anticipation of the subsequent description and discussion, it may be said that all three gave patterns of apatite (calcium phosphate) and in only one was gypsum also present.

Clinical Description

The focal areas of sclera translucency are commonly present in persons in the 9th and 10th decades but are rarely found prior to the 7th decade. Although it has been claimed that they are significantly associated with osteoarthritis[7] (an intriguing suggestion, since they appear to be related to the insertion of the recti muscles), no controlled series has been presented which would prove or disprove this point. The one case associated with porphyria[2] appears to have been unique. The alleged similarity to scleromalacia perforans is hard to accept on the evidence presented, and the resultant confusion has done much to retard the recognition of the entity as a process *sui generis*.

The focal areas are usually manifest as slate-gray spots between the limbus and the tendinous insertions of the lateral and medial recti. A similar area is said to have been seen once anterior to the insertion of the inferior rectus,[8] but in our cases they were limited to the palpebral fissures in the vicinity of the horizontally acting muscles. They are generally very symmetric in the two eyes, but in one of our cases, which had hemorrhagic glaucoma, the scleral translucency was considerably more marked in the glaucomatous eye.

The areas are sharply demarcated, forming in general a vertical ellipse, but vary greatly in size and extent. There is no characteristic abnormality of the vascular pattern or of the overlying conjunctiva. When the area is extensive it often contains a calcific plaque (Fig. 1) that can be visualized in a bone-free roentgenogram (Fig. 2). Even when extensive, these areas of scleral translucency do not ordinarily result in perforation, staphyloma, ulceration, or other deformation of the eye. The frequent statement that the areas are thin is apparently inferred simply from the translucency. The narrow slit-lamp beam does not bear out any indentation of the sclera or provide other evidence of thinning.

Pathology

Most of the observations on the following 30 specimens of scleral translucency were made on tissue in which the translucent area had been excised along with a rim of adjacent sclera. The tissue was fixed in neutral formalin or in alcohol. It was then sectioned in the frozen state after

Fig. 1.—Unusually marked area of scleral translucency situated just in front of the insertion of the lateral rectus muscle. Noteworthy is the white (calcific) plaque situated in the central portions of the translucent area. (The bright highlights are reflections of the flashlight from the surface of the cornea and conjunctiva.)

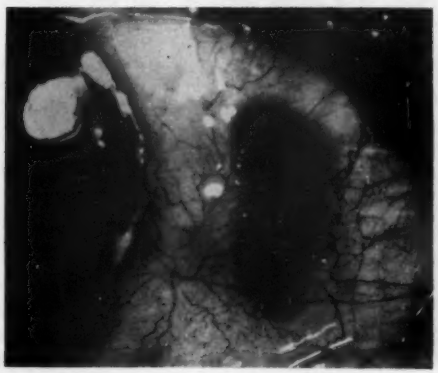
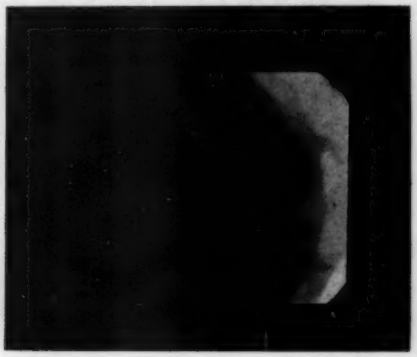


Fig. 2.—Bone-free roentgenograms showing the calcific plaque in the foregoing case.



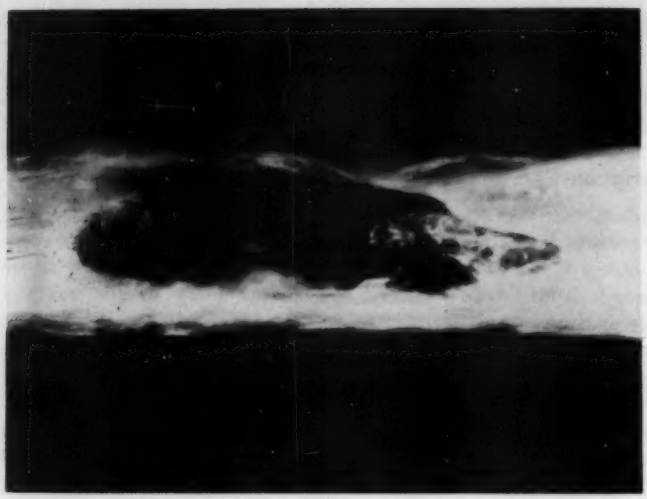


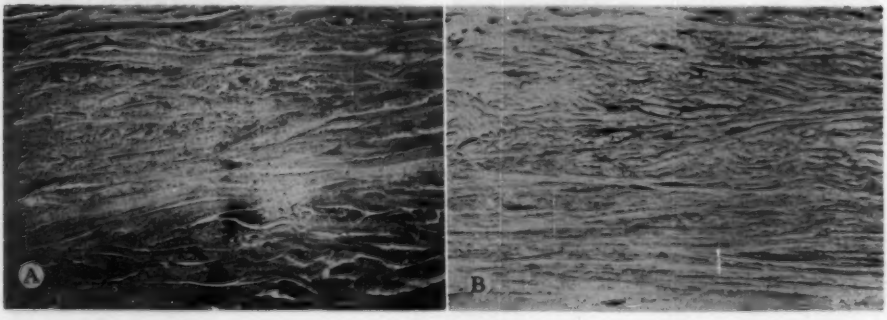
Fig. 3.—Bloc of scleral tissue in which the area of translucency has been bisected and photographed against a black background. The conjunctival surface of the sclera is uppermost in the photograph.

gelatin-embedding and in the nonfrozen state after paraffin-embedding. Routine stains used were Sudan and hematoxylin, hematoxylin and eosin and von Kossa. Selected cases were stained with periodic acid-Schiff, cresyl violet, Van Gieson, Masson, Millon's, and Baker's acid hematein. Sections were also examined in the unstained state for thickness, birefringence, and fluorescence.

In the gross, the sclera showed no thinning. The involved area was translucent, taking on the illumination of the background (Fig. 3). When calcific plaques were present the involved area was characteristically brittle, and the plaque could be shelled out as, in Culler's words, a "seed-like mass." The plaque then had a glass-like appearance which contrasted with the mat opacity of the adjacent sclera. Sections of tissue which contained the calcific plaque showed considerable fragmentation and artifactual distortion of the tissue.

Cross sections of fresh tissue in our cases showed a thickness of the sclera in the region of translucency that was either normal or slightly greater than normal

Fig. 4.—*A*, cross section in the region of scleral translucency showing the absence of cells in a decalcified specimen. Sections were cut in the frozen state and stained with hematoxylin. The dark area extending vertically represents the edge of the former calcific deposit (Oc. 10; obj. 16). *B*, cross section in a corresponding region of a normal sclera showing the usual cellularity of the sclera. The sectioning and staining of this specimen were the same as that of the preceding specimen (Oc. 10; obj. 16).



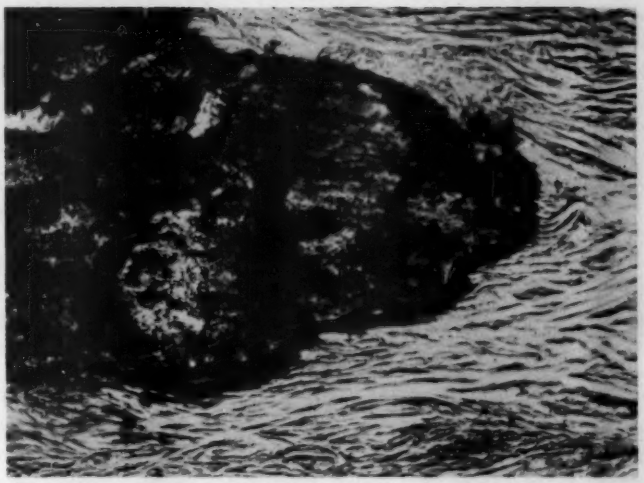


Fig. 5.—One end of a calcific plaque, stained with hematoxylin, showing the basophilia of the plaque and absence of cells in the adjacent sclera (Oc. 10; obj. 16).

(Fig. 3). This is contrary to the clinical and pathologic reports of others that the sclera is abnormally thin in the involved area.

The one constant pathologic abnormality present in all of our cases was a loss of cellularity in the region corresponding to the translucent area (Fig. 4). However, the sclera is normally a cell-poor tissue in the elderly, and this further reduction in cellularity might well pass unnoticed unless special attention were directed to the area which had shown the abnormal translucency beforehand. Despite this loss in cells, the collagenous fibers showed normal birefringence and no hyalinization. This was true even in the cases which had been markedly calcified, provided that the tissue had been decalcified before cutting the sections.

The staining of the collagenous fibers was normal except for some increased basophilia in those cases which had been calcified. No hyalinization was present in any of the involved areas.

The second most characteristic feature in the pathology of focal senile scleral translucency was the plaques of calcification (Fig. 5). This is to be differentiated from the diffuse scattering of calcific granules so common in the sclerae of elderly people (Krekeler[9]). The plaques were present in less than half the cases studied, so they are not an essential part of the entity, but the more extensive the translucent area the more likely was it to be calcified. Hence it would appear that calcification was a secondary, and probably late, sequela of the loss of cellularity.

The calcific plaques consisted of deeply basophilic granules that induced a strong von Kossa reaction (Fig. 6) and only a weak birefringence. They were slightly fluorescent. The calcium dissolved in weak acid solution more readily than was the case with bone or calcified plaques in arteriosclerotic vessels. The acidification with 1 N hydrochloric acid was accompanied by only a slight effervescence of gas (in contrast to arteriosclerotic plaques which showed considerable effervescence), whence carbonates must comprise a negligible portion of the anion. In decalcified specimens, the collagenous framework appeared normal.

In view of our previous finding that one of these plaques consisted almost entirely of gypsum (calcium sulphate),[6] we obtained crystallographic patterns on three additional cases which were morphologically similar to the previous case. All three showed predominantly apatite (calcium phosphate), but one showed gypsum as

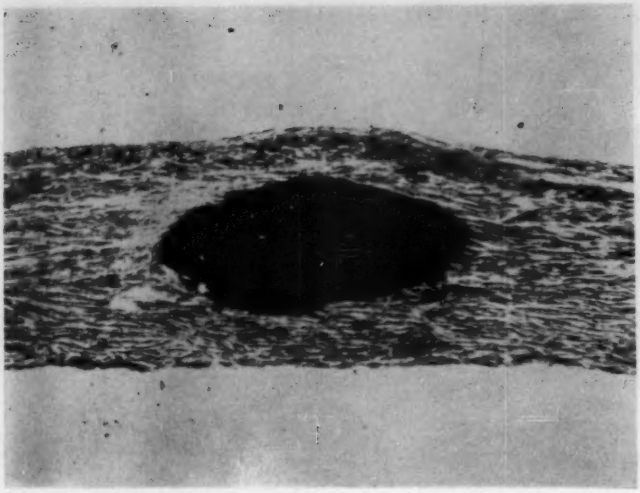


Fig. 6.—Calcified plaque, stained by the von Kossa method, in the center of an area of scleral translucency (Oc. 10; obj. 25).

well, estimated at approximately 10%.* To be sure, the initial case differed from the other three in having been from a glaucomatous eye obtained at surgery, while the others were from normal eyes obtained at autopsy, but this difference could scarcely account for it. We have checked with the crystallographic laboratory and been assured that there could have been no mix-up of specimens. Nor was the eye exposed during fixation to solutions containing appreciable amounts of sulphate. The discrepancy between the first and subsequent specimens seems mysterious but genuine.

Fat stains, done for the first time in cases of focal scleral translucency, showed nothing selectively abnormal for the involved area. A widespread sudanophilia was present in practically all the specimens, as is usual for advanced age, but this was no more conspicuous in the translucent zone than elsewhere. Nor was there evidence that it was more marked in those cases with calcification than in those without calcification.

Conventional polysaccharide stains showed no abnormality. The periodic acid-Schiff reaction was the same as that in the rest of the sclera, and cresyl violet induced no metachromasia.

* For the crystallography and interpretation we are indebted to Prof. Cornelius Hurlbut, Department of Mineralogy, Harvard University.

Comment

Focal areas of translucency in the sclera are so common as to be considered a normal occurrence in the elderly. Their pathogenesis is obscure. There is no direct evidence to support the suggestion that they are due to arteriosclerosis except that both are apt to be correlative functions of age. Arteriosclerosis in the young, as occurs in association with hypercholesteremia, is not associated with changes in the sclera. The constant localization of the translucent area in front of the insertions of the medial and lateral recti has logically given rise to a mechanistic thesis, but crucial evidence for or against such a possibility has not been presented. Such evidence might be the development, or failure in development, of the scleral translucent zones in eyes with life-long palsies of one lateral rectus muscle where the mechanical forces would be expected to be different in the two eyes.

A further suggestion was offered by Fischer [10] and later by Gasteiger,[11] in view of what they considered to be an analogous condition occurring in animals' eyes exposed to air or to hypertonic solutions, to

the effect that evaporation resulted in a deturgescence and focal transparency of the sclera. This, however, was a transient occurrence and differed from the stationary condition in human beings wherein it makes little difference whether the eyes are exposed to air or covered by the lids. Nor have we affected the native area of translucency by soaking the enucleated eyes or excised pieces of sclera in saline solution for several hours.

Whatever their pathogenesis, the scleral translucent zones are characterized histologically by early loss of cellularity and later by calcification. The concept of hyalinization, which has grown in stature by repetition, was not borne out by the present studies. The translucent zones showed normal fibrillary structure of the collagenous fibers clearly unlike true hyalinization, such as occurs typically with radiation or sequestration.

Calcific plaques are common late occurrences in the zones of scleral translucency. The surprising finding in one case that they consisted of gypsum was not borne out in three other cases, where the calcium salt was found to be chiefly apatite.

These plaques occurring with focal areas of scleral translucency are identical with those described by others (Pagenstecher,[12] Katz,[13] Lewi,[14] Klien-Moncrieff,[15] and Friedenwald et al.[16]), where scleral translucency was not noted to have been present or absent. However, in all these cases the calcific plaque overlay the pars plana of the ciliary body, and in several instances it was noted to have been just anterior to the insertion of the horizontal rectus muscles (as in the case with plaques in zones of scleral translucency). Similarly seven cases in our pathologic collection that were cross referenced as "calcific plaques" were reviewed. These were cases of eyes removed for glaucoma or other ocular disease in which the scleral translucent zones were not noted to have been present or absent. All but one of these showed the calcific plaques situated just in front of the horizontal rectus insertions, and in several of these it was continuous with the tendons. In one specimen the plaques were present on both the nasal and temporal sizes (Fig. 7). The plaques were identical with what others have described as calcific plaques in pathologic specimens and what we have described in association with focal senile translucency of the sclera. The one of the seven which was an exception was from an eye in which the plaque was situated behind the equator on the nasal side, not associated with any of the extraocular muscles. The patient also differed from the others in that he was not elderly and, what may be most significant, he had a sarcoid-induced hypercalcemia and metastatic calcification elsewhere.

Thus it would appear that the cases recognized as calcific plaques in the sclera are usually identical to those which occur with focal senile translucency of the sclera. It is entirely possible that the translucent areas were so insignificant clinically as to have escaped notation in the protocols.

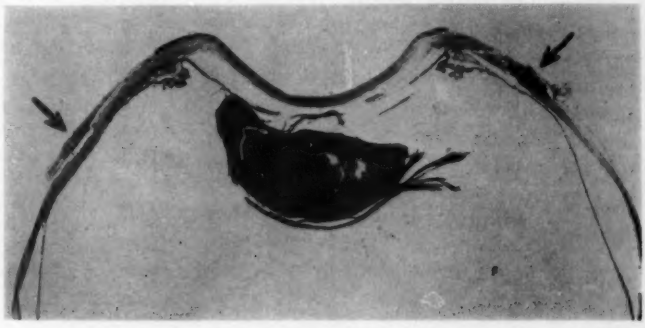


Fig. 7.—Anterior segment of an eye removed because of painful glaucoma, showing discrete foci of calcification in front of the insertions of both the medial and lateral rectus muscles. It is suggested that this finding in routine eyes probably corresponds to areas of focal scleral translucency. (The indentation of the cornea and lens is a fixation artifact.)

Conclusions

1. Focal senile translucency of the sclera is a common occurrence in the elderly and is not known to have clinical significance. The involved areas are almost invariably in front of the tendinous insertion of the medial and lateral recti.

2. Initially the translucent areas show loss of cellularity and later calcific plaques. Contrary to previous reports, we did not find hyalinization. The calcific plaques are identical with calcific plaques heretofore noted as incidental pathologic findings in routine eyes.

3. Although the calcific plaque in one case was found to be gypsum (calcium sulfate), crystallography in three subsequent cases showed the plaques to be composed mainly of apatite (calcium phosphate) although gypsum was also present to a small extent in one of these three cases.

243 Charles St. (14).

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Relative Resistance of Slow-Growing Strains of Toxoplasma Gondii to Pyrimethamine (Daraprim)

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Both Eyles [1] and Summers,[2] working independently, discovered that pyrimethamine (Daraprim) cured acute experimental toxoplasmosis in mice. A subsequent study of the action of pyrimethamine and sulfadiazine [3] revealed that in mice infected with moderate inocula of RH-strain organisms (less than 20,000 parasites) the drugs acted synergistically and were toxoplasmicidal, when given early enough in the course of infection. When larger inocula were used, however, the same combination of pyrimethamine and sulfadiazine, at the highest doses tolerated, did not kill all the parasites, although the mice survived. Similarly, Cook and Jacobs [4] noted that, while pyrimethamine was generally toxoplasmicidal at a concentration of 0.3 mg. % when tested against RH-strain organisms in monkey-kidney tissue cultures, occasionally some organisms remained alive. They reported also that nonproliferating parasites, suspended in tissue culture medium without cells, were apparently unaffected by the drug. Cook then developed a strain of RH toxoplasmas resistant to pyrimethamine in vitro but not, apparently, in vivo.[5] No definitive information was obtained elucidating the mechanism of resistance, but she postulated that dormant organisms might be present in the cultures and be resistant to the drug.

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From the Ophthalmology Branch, National Institue of Neurological Diseases and Blindness (Dr. Kaufman), and the Laboratory of Tropical Diseases, National Institute of Allergy and Infectious Diseases (Drs. Remington and Jacobs, and Miss Melton), National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

Kaufman, Remington, and Jacobs [6] found that, although there was some variation in the apparent rate of multiplication within each strain, the mean rate of multiplication of the virulent RH strain of toxoplasmas in tissue culture was 2.5 times that of the relatively avirulent 113-CE strain. Since it is possible that drug sensitivity is related to the metabolic rate of the parasites, it was of interest to determine the relative resistance of the RH and 113-CE strains to the toxoplasmicidal effects of pyrimethamine in tissue cultures.

Methods

Toxoplasmas of both the RH and 113-CE strains were maintained in chick embryos, harvested from ground chick chorioallantoic membranes, and counted in a Neubauer-Levy counting chamber. The suspension of organisms was appropriately diluted with lactalbumin hydrolysate medium, and 200,000 organisms in 1 ml. of medium were inoculated into each of a series of monkey-kidney monolayer tissue cultures.[6,7] In some experiments the RH and 113-CE were tested in parallel sets of tubes at the same time. In other experiments the strains were tested separately; here, as above, the drug solutions used were identical. The culture tubes were washed out with fresh medium after three hours of exposure to the parasite. Fresh lactalbumin hydrolysate medium, containing an appropriate concentration of pyrimethamine, was then added. The tubes were replaced in stationary racks and reincubated for five to seven days.

Lysis of the tissue cultures did not occur in the tubes containing drug. In order to

TABLE 1.—*Results of Inoculation* *

Experiment No.	Pyrimethamine Conc., Mg. %	Exposure to Pyrimethamine, Days	113-CE Strain		RH Strain	
			No. Mice Killed by Toxoplasmas	No. Mice Alive	No. Mice Killed by Toxoplasmas	No. Mice Alive
I	Control	5	2	3	5	0
	0.1	5	3	2	1	4
	0.5	5	3	2	0	5
	1.0	5	5	0	0	5
II	Control	5	--	--	5	0
	0.3	5	--	--	0	5
	0.5	5	--	--	0	5
	1.0	5	--	--	1 †	4
	5.0	5	--	--	0	10
III	Control	5	2		5	0
	0.3	5	3	2	0	10
	0.5	5	1	5	0	5
	0.5	7	5	0	0	5
IV	Control	5	--	--	5	0
	0.1	5	4	2	4	2
	0.3	5	--	--	0	10
V	Control	5	0	1		0
	5.0	5	1 †	10	1 †	10
IV	Control	5	0	2	--	--
	0.3	5	2	2	--	--
	0.5	5	2	3	--	--

* Into mice, suspensions of monkey kidney epithelium tissue cultures infected with strain 113-CE or RH of Toxoplasma gondii and incubated in the presence of pyrimethamine at various concentrations for five to seven days.

† Toxoplasmas were not demonstrated in the dead mice.

determine whether organisms remained alive after exposure to drugs, the cultures were scraped off the tubes with a rubber policeman, and both the cells and media were inoculated intraperitoneally into N. I. H. general-purpose mice. Mice were kept six weeks after inoculation, and all mice that died were examined for the presence of toxoplasmas. In all but a few cases, which are indicated in the Tables below, the infection was confirmed by microscopic examination of peritoneal fluid and/or impression smears of brain and spleen.

Results

Table 1 presents the results of individual experiments, and Table 2 presents a summary of comparable data. It is apparent from these Tables that when control, nontreated, infected cultures were inoculated into mice, the cultures infected with the 113-CE strain killed only 64% of the inocu-

TABLE 2.—*Summary of Results* *

Pyrimethamine Conc., Mg. %	113-CE			RH			Probability
	Mice Alive	Mice Dead (Parasites Alive)	Total 113	Mice Alive	Mice Dead (Parasites Alive)	Total RH	
Control	4	7	11	0	28	28	
0.1	4	7	11	6	5	11	
0.3	4	5	9	25	0	25	$P<0.001$
0.5	5	11	16	15	0	15	$P<0.001$
1.0	0	5	5	15	1	16	$P<0.001$
5.0	10	0	10	29	1	30	

* At concentrations from 0.1 to 1.0 mg. % significantly more mice survived when inoculated from treated RH-infected cultures, indicating that pyrimethamine more consistently killed these rapidly growing organisms.

lated mice. This is in contrast to the cultures infected with the RH strain, which killed 100% of the inoculated mice. These data agree with previous reports on these strains [8] and confirm that viable organisms of the rapidly dividing RH strain are uniformly lethal for mice but those of the slow-growing 113-CE strain are not.

Despite the fact that the 113-CE organisms do not regularly cause the death of infected mice, the data indicate that when strain 113-CE is exposed to pyrimethamine in concentrations that kill the rapidly growing organisms of the RH strain, some 113-CE organisms survive. Suspensions prepared from cultures infected with 113-CE organisms killed significantly more mice than those from cultures infected with the rapidly growing RH organisms after both sets of cultures had been exposed to drug concentrations between 0.1-0.5 mg. % for five to seven days. Concentrations of 0.1 mg. % do not reliably kill either strain, and concentrations of 5 mg. % kill both strains.

It may be noted that for strain 113-CE the data show less deaths among mice inoculated from the controls than from the cultures treated with drug dosages of 0.1-0.5 mg. %. This is believed to be due to the variability of results usually obtained with this strain.[8]

Comment

Substances that act as metabolic antagonists are used clinically to kill both bacteria and malignant cells but are more effective when the organisms or cells are dividing rapidly.[9] Since pyrimethamine acts as a metabolic antagonist competing in the folic acid pathways involved in nucleic acid synthesis,[10] it is not surprising that slowly multiplying toxoplasmas are more resistant to the drug. If this increased resistance to the drug of the slowly multiplying organisms were slight, it might be masked by the lower invasiveness of the 113-CE strain (with equal inocula, only one-fifth as many 113-CE as RH organisms appear to penetrate into the cells, so that initially there is only one-fifth the *intracellular* inoculum of 113-CE compared to RH) and by the lesser ability of viable 113-CE organisms to kill mice. The difference in susceptibility of the strains to the effects of pyrimethamine is so striking, however, that, despite factors tending to mask this difference, the greater resistance of the slowly growing organisms is apparent even when no statistical corrections for the initial strain differences are applied.

Toxoplasmas that are relatively avirulent for mice have been isolated from human cases of toxoplasmosis, and previous work suggests that such avirulent organisms multiply slowly.[6] Armstrong and MacMurray found that an organism isolated from an excised human axillary gland initially required 84 days to produce death in mice.[11] Beverley points out that "toxoplasmas from man often prove of low virulence for, and fail to produce obvious illness in, laboratory animals; yet toxoplasma cysts may be found in their brains a month or more after inoculation." [12] Siim, in describing his isolations of toxoplasmas from human cases, states, "the infection only rarely kills the animals, but most often runs a subclinical course." He finds it necessary to do dye tests on the mice and multiple subinoculations in order to demonstrate the parasite.[13] Fair [14] and Hogan [15] mention that congenital cases of toxoplasmosis can be dormant and have recurrences late in life, and Hogan suggests that "some cases of inapparent congenital (ocular) toxoplasmosis with late exacerbations of the disease are caused by toxoplasma strains of low virulence," as in the case from which he recently isolated an organism. It seems possible, therefore, that slow-growing organisms are most commonly responsible for human toxoplasmosis, and many of these strains appear less virulent than the 113-CE strain.

Previous studies indicate that a concentration of 0.3 mg. % of pyrimethamine is safely attainable in the serum of patients treated with the drug.[16] In vitro a concentration of 0.1 mg. % did not regularly kill

the organisms of either strain, and only in a concentration of 5.0 mg. % were both strains killed. If the in vitro and in vivo effective concentrations were strictly comparable, the maximum concentration obtainable in the serum, and presumably in the retina, would be near the minimal toxoplasmicidal concentration. Extreme caution is necessary in interpreting the meaning of these in vitro experiments, however. Cook demonstrated that a strain of toxoplasma could be developed which was resistant to pyrimethamine in vitro, though not apparently in vivo.[5] Though the concentration of pyrimethamine reached in vivo was not determined, this suggests that in vivo and in vitro conditions may not be comparable. In addition, when pyrimethamine and sulfonamides are used together, the synergistic activity would be expected to increase the efficacy of the pyrimethamine. This synergism combined with more prolonged therapy may add to the toxoplasmicidal activity of pyrimethamine as used in man. On the other hand, human toxoplasmosis can be caused by organisms which multiply much less rapidly than the 113-CE strain and may be even more resistant to therapy than the strains studied. It is unfortunate that the relationship of these variables to therapy cannot be better defined at present.

Although other mechanisms of drug resistance may exist in cases in which clinical toxoplasmosis appears resistant to pyrimethamine therapy, the possibility that this resistance is related to infection by very slowly multiplying parasites must be considered. The uncertainty of our knowledge of the necessary therapeutic dose of these medications suggests that the largest dosage consistent with acceptable levels of toxicity should be administered.

Summary

Slowly multiplying 113-CE strain toxoplasmas are more resistant to the toxoplasmicidal effects of pyrimethamine (Daraprim) in tissue culture than organisms of the rapidly multiplying RH strain.

The therapy of human toxoplasmosis is discussed in relation to these findings. The concentration of pyrimethamine that can be safely reached in the serum of man is not greater than the minimum concentration required regularly to kill organisms of both strains under the in vitro conditions studied. Many considerations suggest that the effective in vivo and in vitro concentrations may not be directly comparable.

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Traumatic Luxation of Lens

A Case Report

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Rupture of the sclera with luxation of the intact lens to the outside of the globe is a rare occurrence. There are very few cases reported in literature, and these are all quoted from the literature of many decades ago. Surpassing the interesting aspects of this case is the lesson in conservation that is gained and the excellent results with use of ultraviolet-light photography.

Report of Case

A 63-year-old patient was first seen in the hospital in 1947. There was a past history of recurrent eye disease since 1940. A diagnosis of bilateral anterior uveitis had been made. For the next 10 years he had been treated for periodic exacerbations of the disease in each eye. The vision in the left eye was light perception only, but the right eye was maintained at 20/50. The intraocular pressure was only 10 (Schiøtz) in each eye. The last treatments for the uveitis were given in 1955. On April 25, 1957, he received a severe blow to the right eye. The patient did not know whether he was struck by the fist or by a hard object held in the hand of his assailant. He was seen at the hospital within an hour. Examination revealed the visual acuity to be practically nil in each eye. There was light perception but faulty projection in the right eye. There was marked edema and ecchymosis of the right upper and lower lids. A subconjunctival hemorrhage occupied the entire globe. The eye was hypotonous. The cornea was elongated and flattened in the horizontal meridian. The picture was that of a ruptured globe.

Slit-lamp examination revealed a marked striate keratitis, absent anterior chamber, hyphema, and a distortion of the pupil which was displaced up and nasally. No red reflex of the fundus could be seen. A diagnosis of rupture of the globe and intraocular hemorrhage was made. However, conservative treatment was decided upon because his other eye was already blind. Treatment consisted of bed rest, systemic and topical antibiotics (chloromycetin parenterally and Neo-Delta-Cortef [a preparation containing hydrocortisone and neomycin sulfate] drops locally). Within five days the lid and conjunctival edema diminished, and for the first time an extruded lens was suspected to lie beneath the conjunctiva in the upper nasal quadrant. The presence of the lens was confirmed by examination under ultraviolet light. No attempt was made to remove the extruded lens, because it seemed possible

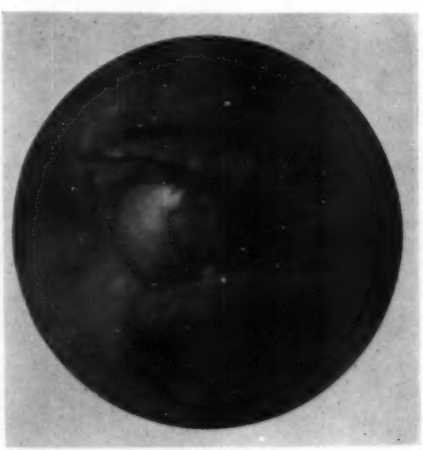

Figure 1

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From the Department of Ophthalmology, Veterans Administration Hospital, Wood (Milwaukee), and Marquette University School of Medicine.

that the lens may have been acting as a plug over the suspected rupture wound in the sclera. After six weeks the hyphema and vitreous hemorrhage cleared. The lens increased in size and was now a dirty yellow color (Fig. 1).

A refraction was done four months after injury. The resultant visual acuity was 20/50, with use of +6.25 +12.00 axis 120.

Comment

Rupture of the sclera with luxation of the intact lens to the outside of the globe is a rare occurrence. Würdemann [1] states, "rupture of the sclera usually occurs within 3 mm. of the corneo-scleral border. Direct rupture is less frequent than indirect rupture, the latter resulting from the globe being drawn against the walls of the orbit being suddenly put under increased tension. Most ruptures occur in the upper inner part of the globe when the eye is forced against the trochlea from below and outward. This rupture is in the so-called meridian of expansion when the tough inner scleral fibers are transformed into the delicate lamellae of the ligamentum pectinatum. This area is about 2.5 mm. behind and concentric to the limbus. The rupture varies from 3 to 12 mm. At either end the rupture usually does not go through on the lamellae." In most cases the eye goes on to destruction, although in Würdemann's case satisfactory vision resulted.

Berliner [2] states: "When a force is applied to the globe, according to hydrodynamic laws, the contents of the eyeball being considered as fluid, the effect of the force is transferred not only in the direction of 'the blow but with equal intensity in all directions.' Therefore, internal pressure develops which acts from the center peripherally so that the intraocular contents are hurled against the wall. . . ."

Duke-Elder [3] states: "In the complete traumatic luxation, the lens may follow different routes—into the anterior chamber, vitreous, subsclerae region, or outside of the eye if the globe is ruptured so that it lies impacted in the rupture itself, comes to rest in the subconjunctival or Tenon's space or is extruded altogether.

"Once the explosive force generated inside the globe by the contusion has burst its envelope, the zonule is completely torn and the solid and relatively heavy lens is readily extruded almost invariably in its capsule (12 out of 13 cases, Mitvalsfy 1897). The actual rupture site may be at the corneoscleral margin or further back over the ciliary body or at the equator. A lens lying subconjunctivally is usually absorbed, its site eventually being marked by calcareous deposits but particularly if the capsule is intact, it may remain practically unaltered almost indefinitely (15 years, Vieusse; 18 years, Collins). The extraocular dislocations usually occur in the upper quadrant somewhat to the nasal side (85% of cases, Souillard, 1910)."

This case apparently follows the line of reasoning of these authors in that the rupture occurred in the upper nasal area, concentric with the limbus and about 2.5 to 3 mm. behind. Of greater significance, of course, is the success obtained by the conservative measures that were employed. A mutilated eye, such as this, might easily arouse the temptation for enucleation, as it actually did to one of our residents. It points out dramatically the fallacy of early surgery in supposedly hopeless eyes.

Figure 2

The extruded lens was spontaneously absorbed in a period of four months (Fig. 2). Since the extrusion of the lens (a period of one year), the patient has had no recurrence of his iritis. However, we do not recommend this as a therapeutic measure. Both photographs were taken by ultraviolet light.

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Use of Gas Sterilization for Ophthalmic Surgery

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In any type of surgery, the ideal method of sterilization should be one that safely permits the sterilization of all instruments, sutures, and drapes as well as plastic and rubber materials together in the same sterilizer. Rusting, corrosion, charring, or deteriorization in any form must not occur even after repeated sterilization. Gas sterilization with ethylene oxide gas is the only method available today that meets all of these requirements. A small portable sterilizer using ethylene oxide gas which is ideal for ophthalmic surgery has been used in these studies.*

Ethylene Oxide Gas

Pure ethylene oxide is both toxic and explosive. The explosive hazard was first eliminated by Phillips and Kaye [1] by mixing the ethylene oxide with carbon dioxide. In the commercial sterilizer used in our studies ethylene oxide has been combined with an inerting agent composed of hydrogenated carbons, and this mixture has been packaged in small containers (Steribulbs) prepared exclusively for use in this sterilizer. This combination may be considered completely safe and absolutely stable.

In order to eliminate the danger of toxicity, the sterilizer has been constructed so that the ethylene oxide gas is completely removed from the chamber by adsorption before the sterilizer is opened. The gas is replaced by sterile fresh air drawn into the sterilizer by a pumping action.

The germicidal action of ethylene oxide gas has been proven by many experimental studies. Kaye and Phillips [2-4] have not only demonstrated the effective killing of a variety of bacteria by ethylene oxide but also have determined the optimum temperature and humidity for bacteriocidal action. No difficulty has been encountered even with the more resistant encapsulated organisms.[5] Numerous studies have been made to demonstrate the effect of the gas on a wide variety of viruses.[6-8] All studies have supported the conclusion that ethylene oxide sterilization is equal or superior to other conventional methods in common use.

Ethylene oxide has numerous advantages over the other methods of sterilization. All instruments and materials may be sterilized together absolutely without alteration. Plastic and rubber materials have been sterilized an indefinite number of times without showing any perceptible effects. Sharp knives and scissors will never rust or become pitted regardless of the metal used for the blade or handle. Although we now have chemical solutions satisfactory for sharp instruments, they still must be rinsed in water before use, and rusting can occur before actual use at the operating table, if not dried immediately by the nurse or surgical assistant. I have even seen a corneal burn from a trephine that was not thoroughly rinsed before use. All of these problems are absent in gas sterilization with ethylene oxide.

Gas sterilization with ethylene oxide has many uses in hospitals other than for the surgical instruments. In the operating room, one of the most valuable nonsurgical uses has been reported by Engley [9] in the absolute sterilization of clinical thermometers. The transfer of infection from one patient to another in hospitals making use of conventional alcohol immersion of thermometers is apparently commoner than formerly

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* Manufactured by the Ben Venue Laboratories, Bedford, Ohio, and available through the leading surgical supply companies.

appreciated. A practical method has been devised to use ethylene oxide to sterilize sheets, blankets, books, and practically any object contaminated by a patient with an infectious disease.[10] The decontamination of objects made and handled by tuberculous patients has been very successful.[5] A large ethylene oxide sterilizer for general hospital use has been described,[11] and others are being designed.

The Ben Venue Sterilizer

This sterilizer is a lightweight, small, cylindrical chamber measuring approximately 7.5×23 cm., with a sleeve-type cover. There is a device for puncturing the small cylinders which contain the gas mixture (Steribulbs). The Steribulbs contain a mixture of ethylene oxide and hydrogenated carbons which, for this purpose, is superior to the ethylene oxide-carbon dioxide mixture used by others. After puncture of the Steribulb, the gas mixture is admitted to the chamber of the sterilizer. The manufacturer has determined that this results in 10 gm. of ethylene oxide per liter of space in the chamber. Sterilization has been found to be complete even for spores and very resistant organisms after two hours.[9,12] This time period is shorter than necessary for some of the larger sterilizers which do not have as good a concentration of the gas.

The ethylene oxide is removed from the chamber of the sterilizer by a unique pumping action. This causes the contents of the chamber to pass through a carbon adsorbent which removes the ethylene oxide, and this is replaced by fresh air filtered through a fine wire mesh and Fiberglass paper. As a result, the sterilizer can be opened without releasing any of the gas into the air of the room. If the directions are followed, there is absolutely no danger to the personnel handling the instruments.

The volume of the sterilizer may be increased by means of an extension tube. This has not been found to be necessary for most of the ophthalmic operations.

The size of the sterilizer is such that two of them can be transported in a brief case. Most of the parts are aluminum, so that it is light in weight. This makes the transportation of the sterilizer complete with instruments no problem, and one may easily take one or more entire surgical setups from one hospital to another or from the office to the hospital.

The Use in Ophthalmic Surgery

The use of ethylene oxide for the sterilization of instruments for ophthalmic surgery has been thoroughly evaluated by Skeehan and his co-workers.[13] In this original study, a steam autoclave was modified to handle the gas. They proved that ethylene oxide gas was practical and effective for sterilization, but the many additional advantages of a small portable sterilizer could not be appreciated. Skeehan [14] has subsequently reported on use of the portable sterilizer used in this study.

Any ophthalmic surgeon who operates in a general hospital has had emphasized the fact that ours is a minor surgical specialty. The time available for operation is usually after other surgery is completed. The nurses or other help assigned to prepare the setup and sterilize the instruments are usually the new, inexperienced nurses, students, or part-time help. It is difficult to orient the auxiliary personnel in the operating room because different ones are assigned at frequent intervals, and one no sooner gets them trained than they are no longer available. As a result, on occasion ophthalmic instruments may be ruined even before being used.

Although the situation is much better in specialized hospitals where eye surgery is common, a similar situation exists for emergency surgery, such as glaucoma surgery or keratoplasty. Invariably, a new nurse or part-time technician is assigned to prepare your instruments who is unfamiliar with them. Although a complete list of the instruments necessary may be available in a book at the operating room, they can not

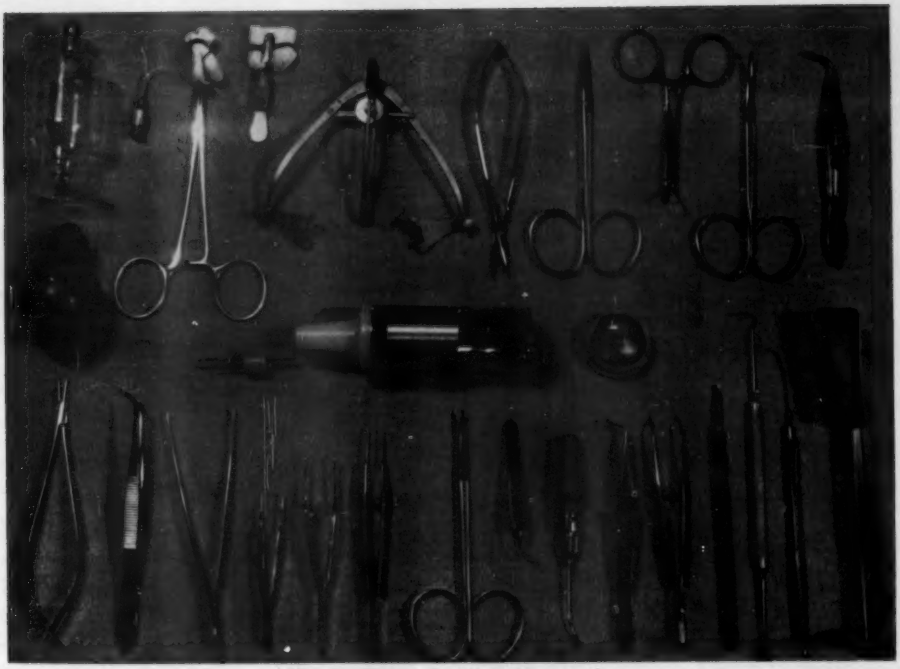


Fig. 1.—Set-up for cataract operation.

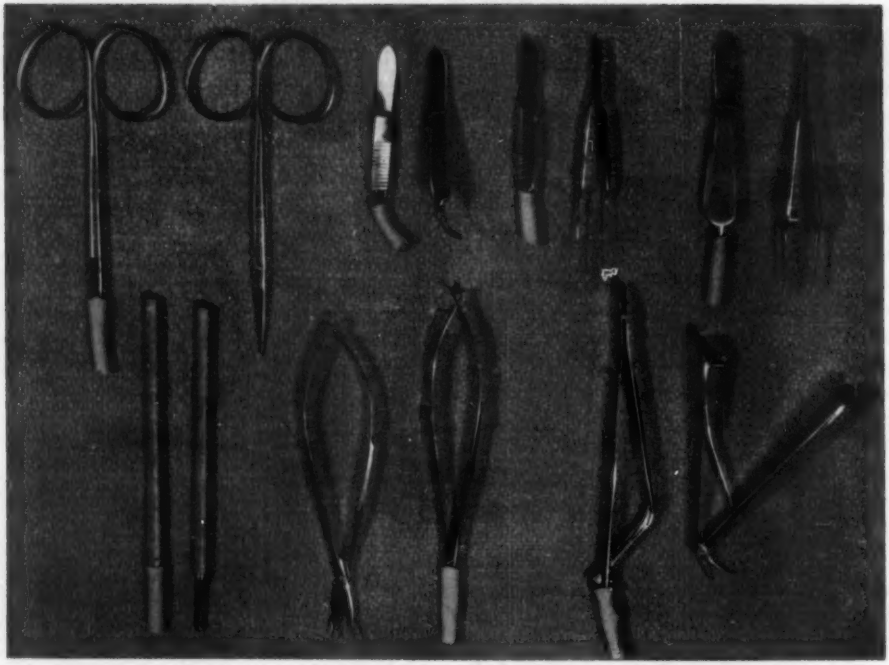
identify or recognize the instruments named on the list. The surgeon, as a result, may appear at the operating room and find that he has few of the instruments necessary to do the job well. He must either proceed with the instruments sterilized or delay surgery until the correct instruments are sterilized.

With the use of a small portable sterilizer, the personnel at the hospital are no longer a problem. The instruments may be selected and sterilized at your office ahead of time and transported in the sterilizer to the hospital ready for use. At the completion of the operation, the surgeon or his assistant may clean the instruments and put them back in the sterilizer ready for the next operation.

All of the instruments used by me for a cataract operation are illustrated in Figure 1. Included in this group are the routine instruments in all setups that may be sterilized by any method. Rubber goods include the bulb for the anterior chamber irrigator and the Esposito erisophake. Plastic material is used in part of the Hildreth coagulator. The sharp instruments, such as cataract knives and scissors, are included. One of the sutures illustrated is a 0000 black nonabsorbable surgical (silk) suture for the superior rectus bridle suture which has been wrapped around a small piece of gauze and clamped in a hemostat. The other suture is a 000000 black silk on a small Grieshaber needle for corneoscleral sutures. This suture is clamped in the Serafine forceps and is contained in the jaws of the Serafine in the illustration. More perfect sterilization is insured if the suture is not in the jaws of the Serafine, as the gas would then have better access to the suture material. These are all the instruments required by me for most cataract operations. Additional instruments can be added to this setup without overloading the sterilizer.

Fig. 2. — The cataract instruments placed in the cloth wrap.

Fig. 3.—The protection of delicate instruments with rubber tubing. Adjacent to each instrument in the illustration is the same or similar instrument with the rubber tubing attached.



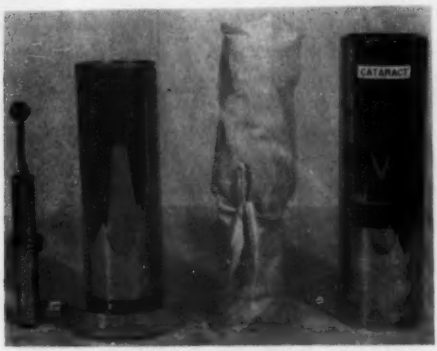


Fig. 4.—The cloth wrap containing the cataract instruments is shown rolled up and ready to be inserted in the sterilizer. This is placed in the base of the sterilizer on the left, and the top, or outer, cylinder of the sterilizer is put in place before puncturing the Steribulb.

A cloth wrap, with pockets to carry these instruments, was designed and made by the staff of Central Supply of the Eye and Ear Hospital.† The instruments for a cataract operation may be seen as they are arranged in the wrap in Figure 2. All sharp instruments are tested before insertion in the wrap for sterilization. Sharp instruments and those with particularly delicate points may be protected by covering the ends with ordinary rubber tubing. An example of the various instruments used in cataract and other eye operations which require rubber tubing for protection is shown in Figure 3. As can be seen, delicate instruments, such as iris forceps, St. Martin forceps, and Holth or Berens punches, may be protected in this way. The sharp points of the iris scissors, whether curved or straight, Beaver knives in the Beaver handle, and Westcott scissors are also protected adequately from damage by the rubber tubing when rolled in the cloth instrument wrap. The usual knife holder for a cataract knife or keratome, as in Figure 1, is ample to protect them. Care must be taken in rolling the wrap and inserting it in the sterilizer because, in spite of the various protective measures described, one could still damage some of the instruments with rough handling. The danger is minimized if this is done by yourself or your trained office assistant instead of hospital personnel. In Figure 4 is shown the cloth wrap containing the cataract setup rolled and ready to be inserted in the sterilizer.

In our office we have three sterilizers filled with instruments prepared for immediate sterilization at all times (Fig. 5). One sterilizer contains sufficient instruments for any glaucoma procedure that we might decide to perform, such as an iridectomy, iridencleisis, or corneosclerectomy. A second sterilizer contains all the instruments necessary for a keratoplasty, with the exception of the trephines which can be selected immediately before sterilization to suit the individual procedure to be performed on that patient. The third sterilizer contains all the instruments necessary for a cataract operation.

† The success of this system of sterilization is largely the result of the careful preparation of these wraps by Mrs. Selma Porter and her staff at Central Supply.

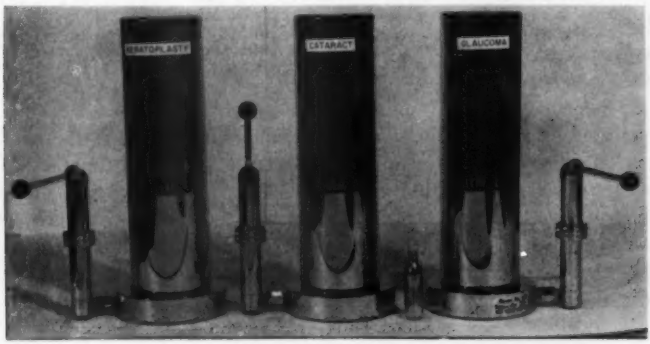


Fig. 5. — Three sterilizers containing complete instrument set-ups. Note the Steribulb adjacent to the middle sterilizer.

In the illustration (Fig. 5), the two end sterilizers are shown with the knob in the down position to which it is pushed in order to puncture the Steribulb. It should not be held in this position but should be immediately pushed back to the vertical position as shown in the middle sterilizer. When it is returned to this position, the escape of the gas mixture is confirmed in two ways: the connection of the Steribulb-piercing assembly to the main sterilizer chamber becomes cold; at the same time, the outer tube of the sterilizer momentarily rises an inch or so on the inner tube, as if it were going to be blown off, only to return to the original down position in a matter of a few seconds. This movement is positive evidence of a free release of the gas into the chamber, and for this reason it is recommended that one should not touch the outer tube when piercing the Steribulb but hold the sterilizer steady at the base.

Gas sterilization with this portable sterilizer has been used for 132 cases of intraocular surgery without a single instance of postoperative infection. Ninety-nine cases were cataract extractions; seventeen cases were keratoplasties, and sixteen cases were glaucoma procedures. Bacteriological studies on the contents of the instruments contained in the sterilizer were performed on several occasions without isolation of any organism. Extensive bacteriological studies were not made because the effectiveness of ethylene oxide and the efficiency of the sterilizer had been already established by thorough studies by other investigators.

Other Uses

Engley [9] has found the Ben Venue Sterilizer to be ideal for the sterilization of clinical thermometers in the hospital. A roll of disposable paper containing individual pockets for each thermometer with a perforated area between pockets can be obtained so an individual thermometer can be removed with its surrounding paper. This represents, without doubt, the safest and most thorough sterilization of clinical thermometers.

We have found the same paper rolls that are used for thermometers to be excellent for the sterilization of allergy syringes used in performing skin tests in uveitis studies. Each syringe so packaged can always be used for the same antigen and is easily marked for that purpose. There is no danger of antigens being mixed.

Comment

The closest to an ideal sterilizer for an individual ophthalmic operation is represented by the portable sterilizer used in this study. Certain precautions must be observed for this sterilizer to be effective. The instruments should be arranged so that the gas vapor has free access to all surfaces. Plastic wraps can not be used, but only gauze or cloth that is penetrated freely by the gas is advisable. The instruments must be cleaned prior to sterilization, because dried blood or other organic debris might interfere with adequate sterilization. The ethylene oxide gas penetrates rubber and plastic, and is retained in them for short periods of time. It is advisable to remove them from the sterilizer one to two hours before use so this absorbed gas can escape.

Gas sterilization will prolong the useful life of the surgical instruments because of the lack of corrosion or rusting. On several occasions the condition of the instruments used in the sterilizer has prompted unsolicited remarks by hospital personnel to the effect that they must be all new instruments because little sign of use is apparent. The instruments prompting such a comment have at times been sterilized weekly for over a year.

The only disadvantage of this sterilizer that has been apparent so far is the time required for sterilization. This time is two hours and would prevent the use of a single set of instruments for another case soon after being used. This disadvantage is less if more than one sterilizer is used. We have, on many occasions, used three cataract setups in a morning, all of which were

contained in separate sterilizers and sterilized the afternoon before at the office.

The greatest advantage of this compact lightweight sterilizer is to the ophthalmologist operating at one or more general hospitals, particularly if he does one or more cases a day at each hospital. Much time will be saved at the hospital, and careless destruction of the delicate instruments is eliminated. The sterilizer is of value in a specialized hospital on many occasions as well, particularly for emergency surgery. We have found it helpful at the Eye and Ear Hospital if we have the sterilized instruments prepared and ready for use when we arrive in the morning, as no delay will result and the operating room personnel will be free to prepare for subsequent cases.

At the present writing, the cost of the small sterilizer may be higher than desirable if the surgeon or hospital desires to purchase several of them. I am sure the cost will be reduced if the demand is sufficient.

Summary and Conclusions

The effectiveness of ethylene oxide gas for sterilization is reviewed.

A small portable sterilizer is described. It is a compact, lightweight sterilizer ideal for use by ophthalmic surgeons, because a complete set of instruments for almost any eye operation can be sterilized together in one of these sterilizers.

The method of use of the sterilizer for ophthalmic surgery is described, including how the more delicate ophthalmic instruments are protected from damage.

This sterilizer is useful for all ophthalmic surgeons but will be particularly valuable for those operating in one or more general hospitals where eye surgery is a small fraction of the surgery performed.

Some uses other than for ophthalmic surgery are mentioned.

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Cyclodiathermy Combined with Medical Treatment in Glaucoma with Severe Visual Field Loss

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In cases of glaucoma not controlled by medical therapy and with small residual fields, there are three choices of treatment:

1. *A filtering operation:* A filtering operation may be successful, but most reports[1-3] have indicated poor results. Relatively minor complications may be disastrous, and even after an uncomplicated procedure there may be a sudden loss of the remaining field or an increase in the rate of progress of lens opacities. Realization of this is conducive to *procrastination.*

2. *A purposeful continuation of medical treatment in spite of uncontrolled ocular tension:* Many writers[4,5] consider this the only permissible treatment for one-eyed patients. In cases where this situation prevails in both eyes, they consider surgery on one eye permissible.

3. Finally, treatment may be by means of *cyclodiathermy,* either alone or, as will be advocated here, *supplemented by continued medical therapy.*

There is now a voluminous literature about cyclodiathermy. Many papers speak unfavorably of it, while others are enthusiastic. However, most imply that further evaluation of its many possible variations are desirable. Castroviejo[6,7] considers cyclodiathermy the operation of choice in chronic noncongestive glaucoma. Scheie, Frayer, and Spencer[8] find it one of the safest approaches to glaucoma and advocate its use in cases with residual fields.

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From the Departments of Ophthalmology of the Royal Victoria Hospital and McGill University.

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This paper is a report of the results of combined cyclodiathermy and medical therapy in 13 eyes with severe visual field loss in which the ocular tension could not be controlled by medical therapy alone.

The series is small because it is limited to (1) cases from my private practice, on whom I was personally able to carry out the treatment and every facet of the pre- and postoperative care; (2) cases where the isopter for 3/1,000 white test object fell within 5 degrees of the fixation point, and (3) cases with a postoperative follow-up period of 12 months and longer. (The average follow-up period is 30 months.) This arbitrary minimum follow-up period was selected because, in a study of 500 cases, Kronfeld and McGarry[2] found that progression of visual fields after normalization of tension became readily apparent within a year.

Since it was possible to follow all patients in this category, the series is a consecutive one and no cases are being excluded.

Tensions in this paper are expressed in terms of the 1955 American Academy scale for Schiøtz tonometers; those recorded before publication of the 1955 scale have been converted to it. I have taken 24 mm. Hg as the upper limit of normal. (All eyes had normal ocular rigidity.) Because of the advanced field loss, postoperative tensions of less than 22 mm. Hg seemed desirable in order to provide a margin of safety and to allow for diurnal variations. Miotics and carbonic anhydrase inhibitors were given as needed to attain this level of control.

Visual field examinations were done by me under uniform conditions. Pupil size,

lens opacities, refraction, emotional status, etc., were given careful consideration.

Gonioscopy was performed preoperatively and postoperatively on all eyes except one (Case 6), where corneal edema and severe asthma made it impractical. Tonography was carried out preoperatively and postoperatively on all but three eyes (Cases 5 and 6), where corneal epithelial changes contraindicated the test. Ocular rigidity measurements were made pre- and postoperatively on all eyes, with use of the 5.5 and 10 mg. weights on the Schiøtz tonometer, because it has been suggested[9] that the reduced tension after cyclodiathermy may be due to lowered ocular rigidity rather than to reduced intraocular pressure.

The Schirmer test and corneal sensitivity measurements were also carried out postoperatively on all patients.

Material

Thirteen eyes in eight patients were studied. Ten eyes had chronic simple glaucoma. (In six the angles were wide, and in four they were narrow; in one of the latter [Case 7], there were peripheral anterior synechiae.) Both eyes of one patient (Case 5) had juvenile glaucoma with hydrophthalmos, associated with other congenital ocular anomalies, and were aphakic as the result of cataract surgery at ages 3 and 7. One eye (Case 6) with long-standing high tension defied accurate classification.

None of the eyes had had previous glaucoma surgery.

Seven of the eleven phakic eyes had lens opacities of mild to moderate degree, judged preoperatively to be acquired and progressive. (The presence of incipient cataracts was viewed seriously, since it was not thought that these fields would stand up well to the circulatory and pressure changes of later cataract surgery.)

In four patients, the eye to be operated on was the only eye with useful vision, the fellow eye having vision of hand-movements or less.

The Table shows the duration of postoperative observation in each case. The shortest postoperative follow-up period was 12 months, the longest 61, and the average 30.

Indications for Cyclodiathermy.—Indications for surgery (cyclodiathermy) fell into three categories:

1. Three eyes were operated on as an urgent measure because of tensions of 60 or higher which could not be reduced medically.

2. Four eyes with tensions consistently between 27 and 34 mm. Hg while on medical therapy were operated on only after observation of continuing field loss.

3. Six eyes with tensions between 28 and 40 mm. Hg in spite of miotics on three or more consecutive occasions were operated on without waiting for evidence of further field loss. The extremely small size of the residual field or the close approximation of one edge of the field defect to the fixation point would not permit further loss without endangering central vision.

Preoperative Preparation and Operative Technique

The operation was done under local anesthesia. Sodium pentobarbital (Nembutal), 200 mg. two hours before operation and 100 mg. one hour preoperatively, and meperidine (Demerol) hydrochloride, 100 mg. intramuscularly 30 minutes before surgery, were usually given.

The tension of the eye with 2% pilocarpine or a miotic of similar strength was used as a guide to the number of cyclodiathermy punctures. DFP was discontinued the day before operation, as it did not seem wise to do the procedure with the eye under such strong miotic effect. Neosporin ophthalmic solution (a preparation of polymyxin B, gramicidin, and neomycin) was instilled several times preoperatively.

Description of Operative Procedure.—The operative technique used was similar to that of Castroviejo.[6,7] Topical 0.5% tetracaine (Pontocaine) drops; retrobulbar injection 2.0 cc. of 2% procaine hydro-

Results of Cyclodiathermy Combined with Medical Therapy in Thirteen Eyes with Glaucoma and Severe Visual Field Loss *

Case	Eye	No. Diathermy Applications	Tensions, Mm. Hg †			Visual Acuities			Visual Fields			Postop. Follow-Up, Mo.
			Preop.	12 Mo. Postop.	Last Exam.	Preop.	12 Mo. Postop.	Last Exam.	Preop.	12 Mo. Postop.	Last Exam.	
1	O. D.	9	30[a]	19[a]	16[a,e]	20/20	20/20	20/20	Fig. 1	No change	No change	47[f]
	O. S.	Not operated on	21	—	—	H. M.	—	—				
2	O. D.	10	32[a]	20[a]	20[a]	20/25	20/25	20/25	Fig. 2	No change	No change	12[g]
	O. S.	10	32[a]	20[a]	20[a]	H. M.	H. M.	H. M.	[c]	No change[a]	No change	12[g]
3	O. D.	12	36[a]	13[a]	17	20/200[d]	20/200[d]	20/300[d]	Fig. 3	No change	No change	19[h]
	O. S.	12	36[a]	13[a]	17	20/80[d]	20/100[d]	20/200[d]	Fig. 3	No change	No change	19[h]
4	O. D.	10	30[a,c]	20[a,c]	20[a,c]	20/60[d]	20/60[d]	20/60[d]	Fig. 4	No change	No change	13[h]
	O. S.	12	32[a,c]	20[a,c]	20[a,c]	20/50[d]	20/50[d]	20/50[d]	Fig. 4	No change	No change	13[h]
5	O. D. (1st operation)	8	30[b,c]	—	—	20/200	—	—	—	—	—	—
	O. D. (2d operation)	8	60[b,c]	17[b,c]	22[b,c]	20/200	20/200	20/200	Fig. 5	No change	No change	19[f]
	O. S.	10	60[b,c]	19[c]	13[c]	C. F. 1 ft.	C. F. 1 ft.	C. F. 1 ft.	Fig. 5	No change	No change	19[f]
6	O. D.	Not operated on	20	—	—	No L. P.	—	—	—	—	—	—
	O. S.	16	56[b]	14[b]	14[b]	C. F.[d] 1 ft.	C. F.[d] 1 ft.	H. M.[d]	[c]	No change[a]	No change[a]	58[f]
7	O. D.	Not operated on	11	—	—	H. M.	—	—	—	—	—	—
	O. S.	8	26[a]	22[a]	19[a,c]	20/25	20/30	20/30	Fig. 6	No change	No change	40[g]
8	O. D.	8	27[a]	20[a]	19	20/25[d]	20/30[d]	20/50[d]	Fig. 7	Slight loss	Further loss (Fig. 7)	61[f]
	O.S	10	30[a]	20[a]	13	20/20[d]	20/20[d]	20/25[d]	Fig. 7	Slight loss	Further loss (Fig. 7)	61[f]

* Isopter for 3/1,000 white test object, within 5 degrees of fixation point. [a] indicates receiving pilocarpine; [b], receiving diisopropylfluorophosphate; [c], receiving carbonic anhydrase inhibitor; [d], acquired lens changes; [e], gross confrontation fields, acuity too low for tangent screen record; [f], still under observation; [g], moved, lost to observation; [h], deceased.

† 1955 Scale for Schiøtz Tonometers.

chloride (Novocain) in 1:40,000 epinephrine with hyaluronidase, 6 turbidity-reducing units per cc.; subconjunctival injection of 2% cocaine,* 2-3 minims (0.12-0.19 cc.) or just enough to raise a small bleb, one at 12 o'clock near the upper fornix and one at 6 o'clock near the lower fornix, keeping infiltrated area well away from region of proposed cyclodiathermy (the procedure is painful if the subconjunctival cocaine is not given); diathermy applied through dry conjunctiva and sclera with 1.5 mm. Castroviejo electrode, 6 mm. behind the limbus; duration of applications, 10 seconds each; current, just enough that entire length of electrode perforates conjunctiva and sclera without pressure (coagulating current of Walker unit used here); 8 to 10 applications in cases where preoperative ocular tension after instillation of pilocarpine is 26 to 32 mm. Hg, 12 to 16 punctures in cases with higher tensions, smaller number of punctures in reoperations†; punctures distributed equally around entire circumference; no miotic or mydriatic instilled at end of operation; Neosone ointment (a preparation of cortisone acetate and neomycin sulfate); single eye dressing, which is removed on first postoperative day.

Comment on Operative Technique.—Details of technique in cyclodiathermy are important. Many different ways of performing the procedure are described. The one term "cyclodiathermy" is in fact used to denote a large number of procedures, so different in their effects and results that they should be regarded as entirely different operations.

The operative results presented here cannot justifiably be compared with those of any other method of cyclodiathermy which does not include (*a*) performing applications through conjunctiva and sclera with a 1.5 mm. electrode, (*b*) site of application not closer than 5 or farther than 7 mm. from limbus, (*c*) applications evenly distributed around the entire circumference, and (*d*) each application of 10 seconds duration.

Factors which cannot be precisely controlled or standardized are variations in the intensity of current employed and in the electrical resistance of the tissues. However, when the intensity of the current is adjusted as described and efforts are made to keep the field dry, a reasonably uniform technique giving remarkably consistent results is attained.

As with any quantitative approach to treatment, experience is needed to learn the results to be expected from variations in the number of diathermy punctures or in the intensity of the current. One of the advantages of the procedure, however, is a considerable margin of effectiveness and safety. Too few applications or too low a current will give an insufficient tension-lowering effect. Too many applications or too strong a current will cause atrophy of the globe, or other serious complications. Between the two extremes, however, considerable leeway in the quantitative aspects of the operative technique is possible. If in doubt, the operator should at first err on the conservative side, since the operation can be safely repeated.

Postoperative Course and Care

Patients in this series were kept in hospital for three to five days after operation for observation, although they could have been discharged the day after surgery. There was no postoperative discomfort. Neosone ophthalmic ointment was used q. i. d. for seven days to combat any mild traumatic uveitis; 2% pilocarpine drops were given q. i. d., beginning at discharge, the eyes being quiet at that time in every

* Castroviejo[6,7] has discontinued use of subconjunctival cocaine in order to maintain dryness of the diathermy bed. He has instead substituted an increase in the volume of retrobulbar anesthetic.

† Castroviejo[6,7] has emphasized the greater danger of excessive effect in reoperations. He advised four applications (one per quadrant) at a second operation and only two applications at a time for subsequent procedures. I have used as many as eight punctures at reoperation, depending upon the height of the tension and the number of punctures already given.

instance. The patients were warned that the sight in the eye operated on would probably be blurred for a day after operation. The vision invariably returned to its preoperative level by the second postoperative day.

My own previous experience had revealed a tendency for the normalized tension to increase slowly during the first few postoperative weeks or months (also observed by Scheie et al.[8] and by Berens[10]).

In this series, to safeguard against a recurrence of hypertension between visits, 2% pilocarpine was prescribed at the time of discharge from hospital, unless there was hypotony (less than 10 mm. Hg). After several weeks or months, when the tension had become stabilized, medical therapy was discontinued if no longer necessary (Cases 3 and 8). It also seemed wise in cases with advanced field defects to keep the tension less than 22 mm. Hg, if possible, in order to provide a greater margin of safety and to allow for phasic variations. Therefore, tensions as low as 19 (7/7.5) were considered indications for the continuation of miotics (usually 2% pilocarpine q. i. d.), and tensions of 22 (6/7.5) with miotics were indications for acetazolamide (Diamox), 250 mg., or dichlorphenamide (Daranide), 50 mg. q. h. s.

Report of Cases

CASE 1 (Fig. 1).—Man, age 80. Right eye, chronic simple glaucoma. November, 1954: first seen because of sudden decrease

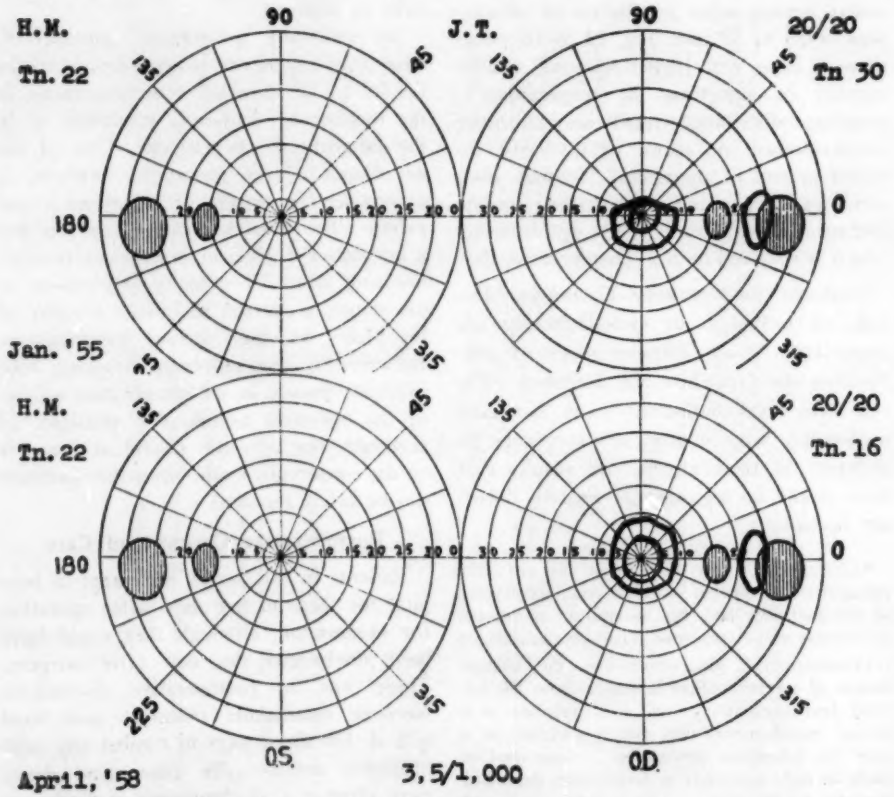

Fig. 1 (Case 1).—Vision, tension, and fields. Upper: at time of operation. Lower: 39 months after operation. (No change eight months later.)

of vision, O. S. Vision: O. D., 20/20; O. S., H. M. Tension: O. D., 33; O. S., 22. Occlusion of inferior temporal branch of central retinal vein, O. S. Glaucomatous cupping; O. U. Media clear. Anterior chambers of moderate depth, angles narrow, no peripheral anterior synechiae. Visual field, O. D.: Residual small central island of vision and a temporal island (Fig. 1). Tension, O. D., remained elevated at 30 on 4% pilocarpine q. i. d., and further loss of field occurred. January, 1955: cyclodiathermy, O. D., nine punctures. December, 1958 (47 months postoperative follow-up): Visual acuity and fields have remained unchanged. Tension, O. D., has varied between 16 and 22. Pilocarpine, 2%, O. U., q. i. d. since third postoperative day. Acetazolamide, 250 mg. q. h. s., since May, 1956. Corneal sensation, O. D., present but reduced as compared to O. S. It is not known whether miotics have been essential in this case, since the eye has not been observed without them. The occasional tension of 22, however, has been sufficient indication for continuing them and suggests that they probably have been needed for full-time control.

CASE 2 (Fig. 2).—Woman, age 58. Both eyes, chronic simple glaucoma. Aug. 6, 1956: first seen with complaint of gradual loss of vision O. U. for two years. Vision: O. D., 20/25; O. S., H. M. Tension: O. D., 32; O. S., 32. Glaucomatous cupping, O. U. Media clear. Wide angles, no

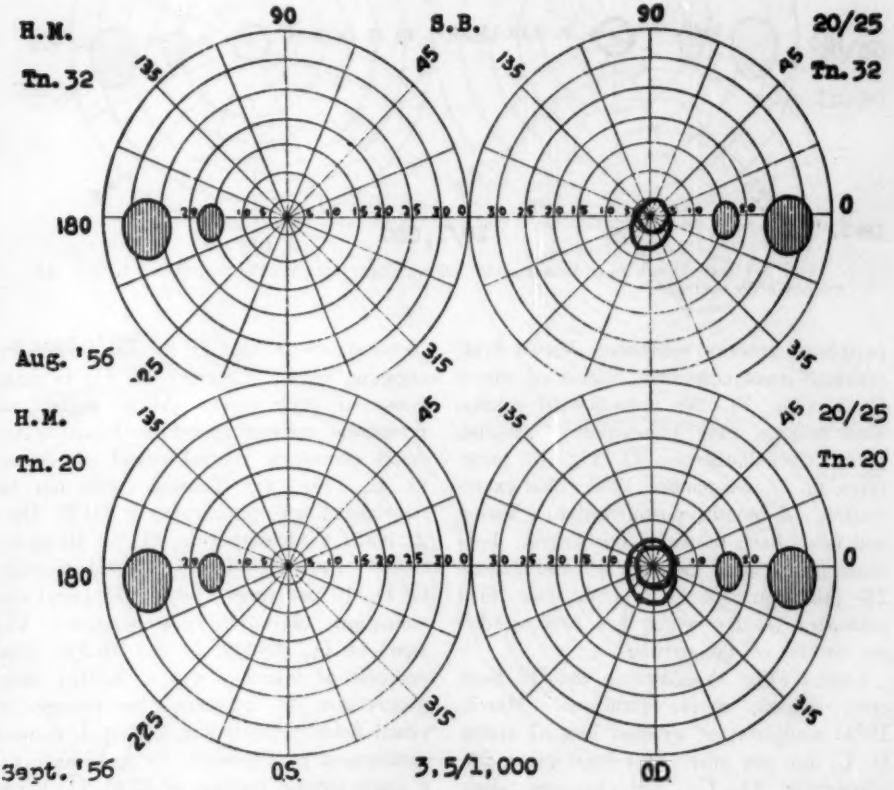

Fig. 2 (Case 2).—Vision, tension, and fields. Upper: at time of operation. Lower: one month after operation. (No change 11 months later.)

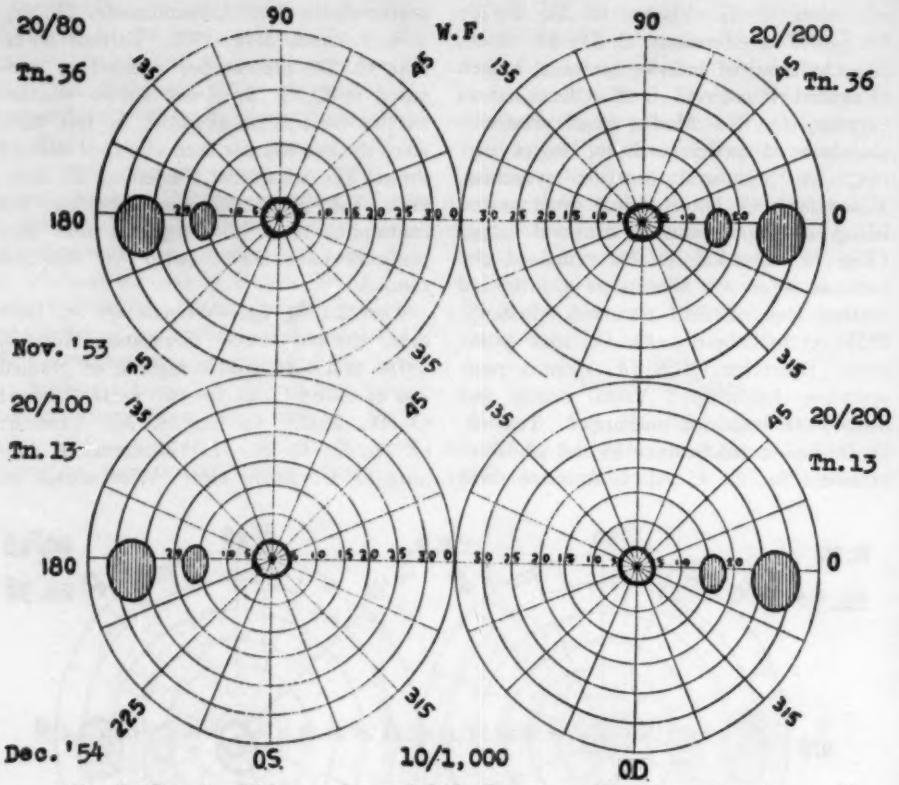

Fig. 3 (Case 3).—Vision, tension, and fields. Upper: at time of operation. Lower: 13 months after operation.

peripheral anterior synechiae. Visual field: residual small concentric island of vision O. S. (Fig. 2). No reduction of tension with miotics (4% pilocarpine). August, 1956: Cyclodiathermy, O. U.; 10 punctures, O. U. September, 1957 (final examination, 12 months postoperative): Vision and fields have remained unchanged. Tensions have varied between 16 and 22, on 2% pilocarpine O. U. q. i. d. since third postoperative day which has been needed for control of the tension.

CASE 3 (Fig. 3).—Woman, age 78. Both eyes, chronic simple glaucoma. March, 1953: complaint of gradual loss of vision O. U. for one year. Has been using 2% pilocarpine, O. U., for glaucoma since 1948. Vision: O. D., 20/200; O. S., 20/80. Tension: O. D., 36; O. S., 36. Pathologic cupping, O. U. Cataract, O. U., is main cause of poor vision. Wide angles, no peripheral anterior synechiae. Visual fields: small concentric central island of vision, O. U. (Fig. 3). Tension could not be normalized with pilocarpine or DFP. Dec. 2, 1953: Cyclodiathermy, O. S., 10 punctures. Dec. 9, 1953: Cyclodiathermy, O. D., 10 punctures. July, 1955 (final examination, 19 months postoperative): Vision: O. D., 20/300; O. S., 20/200. The decrease of vision is due to further slow progression of cataracts. No change in visual fields. Pilocarpine, 2%, q. i. d. was commenced in February, 1954, because of a single tension reading of 22 O. U. With this exception, postoperative tensions have

been between 14 and 19. The pilocarpine was discontinued in March, 1955, because it was aggravating the visual problem. Tensions continued in the same range. Postoperative miotics were probably unnecessary in this case. Corneal sensitivities diminished but present O. U. Patient died in August, 1955, of cancer of the bladder.

CASE 4 (Fig. 4).—Woman, age 71. Both eyes, open-angle glaucoma (Fig. 4). March 25, 1957: first seen with complaint of blurring of vision for six months. Vision: O. D., 20/60; O. S., 20/50, which did not improve on medical treatment. Tension: O. D., 44; O. S., 41. Glaucomatous cupping, both eyes; early cataracts, both eyes. Anterior chambers of moderate depth, angles narrow. Irregular visual fields, with one edge threatening fixation point (Fig. 5). Average tension with miotics (4% pilocarpine, 0.05% DFP, and dichlorphenamide) O. D. 30; O. S. 32. April 29, 1957: Cyclodiathermy, O. U.; 10 applications, O. D.; 12 applications, O. S. April 30, 1958 (final examination, 12 months postoperative): tension: O. D., 20; O. S., 20, with 4% pilocarpine O. U. q. i. d. and dichlorphenamide, 50 mg., b. i. d. Vision: O. D., 20/60; O. S., 20/50. No apparent progression of cataracts. Visual fields (Fig. 4) the same or slightly larger than preoperative fields. The patient had been placed on dichlorphenamide in December, 1957, because of tensions of 22 O. U. on two successive occasions. After this, the tensions remained at safer levels. Postopera-

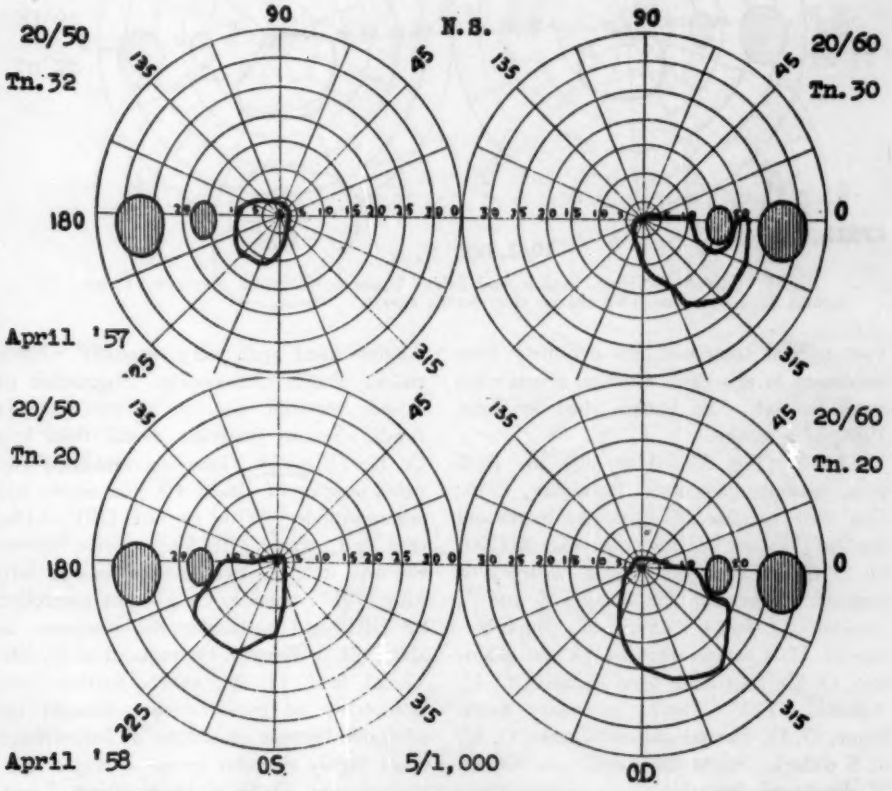

Fig. 4 (Case 4).—Vision, tension, and fields. Upper: at time of operation. Lower: 12 months after operation.

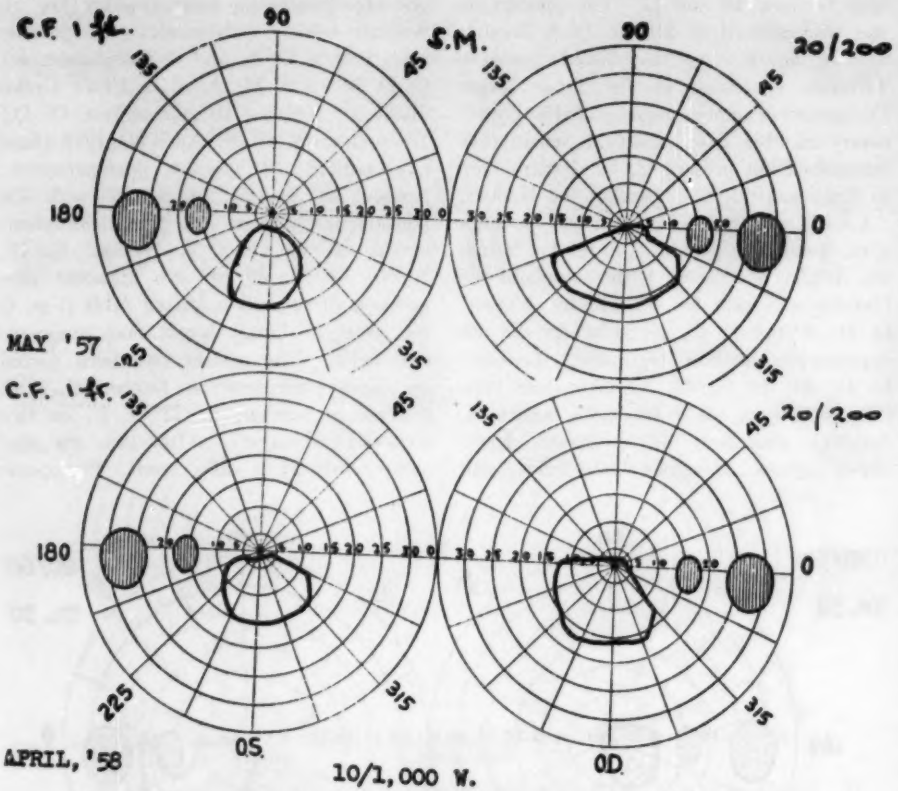

Fig. 5 (Case 5).—Vision, tension, and fields. Upper: at time of operation. Lower: 11 months after operation. (No change nine months later.)

tive medical treatment has definitely been necessary in this case. Corneal sensitivities were normal. The patient died in June, 1958, of a stroke.

Case 5 (Fig. 5).—Man, age 23. Both eyes, juvenile glaucoma. December, 1956: first seen because of gradually increasing loss of vision. Vision: O. D., 20/100; O. S., counting fingers at 1 ft. History of cataract surgery O. U. at ages 3 and 7. Tension: O. D., 43; O. S., 37. Buphthalmos O. U. Corneas measure 13 mm. diameter, O. U. Beginning band keratitis, O. U. Aphakia, O. U. Partial secondary membrane, O. D. Partial iris colobomata, O. U. at 6 o'clock. Slight flare and cells, O. U. Moderate number of coarse vitreous opacities, O. U. Anterior chambers deep. Angles filled with very vascular whitish tissue. Fundi seen poorly. Suggestion of raised, elevated whitish lesions seen in fundi. Severe irregular visual field loss O. U. (Fig. 5). Tensions remained elevated in spite of use of 4% pilocarpine and acetazolamide. With use of DFP 0.1%, eyes first became soft; later tension became elevated in right eye and normal in left. May, 1957: tension, O. D., not controlled by DFP and acetazolamide; continues at about 30. Vision, O. D., reduced to 20/200. Visual field, O. D., shows further loss. Goniotomy or goniopuncture thought inadvisable because of danger of hemorrhage from highly vascular tissue in angle. Cyclodiathermy, O. D., eight punctures, 7 mm. behind limbus. Postoperatively tension in

each eye remained about 12 on 0.1% DFP, t. i. d., until July 21, 1957, when patient awoke with pain, redness, and decrease in vision in both eyes. Tension: O. D., 60; O. S., 60. The sudden rise in tension could not be reduced by DFP and acetazolamide in hospital. July 23, 1957: Cyclodiathermy, O. U., 8 punctures O. D., reoperation; 10 punctures, O. S. Feb. 9, 1959 (last examination, 19 months after second operation): no change in vision or fields. Tensions have remained between 12 and 22, O. U., on 0.1% DFP, O. D., and dichlorphenamide, 50 mg., q. i. d. Corneal sensitivities normal, O. U.

Case 6.—Man, age 69. Left eye, advanced neglected glaucoma of uncertain classification. July 14, 1953: first seen complaining of pain in O. S. No vision in right eye, since antiglaucoma operation 20 years previous. Vision: O. D., no light-perception; O. S., counting fingers at 1 ft. in temporal field only. Tension, O. S., 56. Cornea steamy. Deep anterior chamber. Posterior synechiae. Moderately advanced cataract. Tension, O. S., remained at 56 on intensive medical therapy, including trial of DFP. Patient refused operation for one week because of loss of vision of fellow eye after glaucoma surgery. July 22, 1953: Cyclodiathermy, O. S., 16 punctures. May, 1958 (58 months postoperative follow-up): vision of counting fingers at 1 ft. in temporal field was maintained for three years. Vision now reduced to hand movements due to progression of cataract. DFP, 0.1%

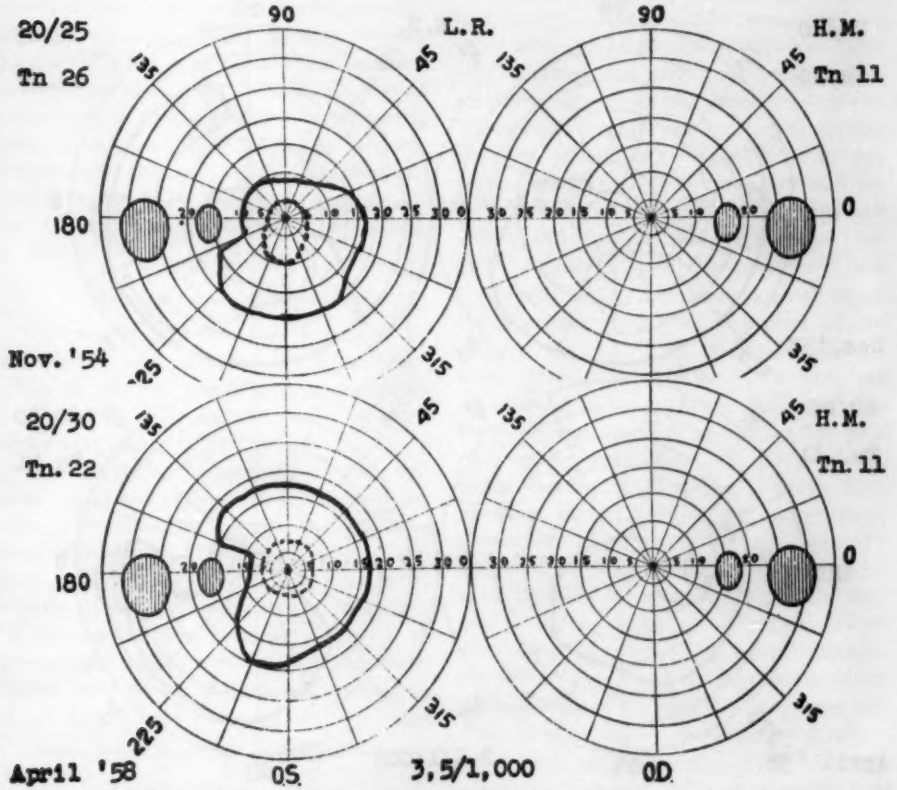

Fig. 6 (Case 7).—Vision, tension, and fields. Upper: at time of operation. Lower: 40 months after operation.

q. h. s., has been required to control tension which has ranged between 12 and 22 with this treatment. Visual field (to confrontation test) appears unchanged. Corneal sensitivity O. S. diminished in comparison with O. D.

CASE 7 (Fig. 6).—Woman, age 53. Left eye, open-angle glaucoma with partial goniosynechiae (Fig. 6). January, 1954: first seen because of headaches. Poor vision, O. D., all her life. Vision: O. D., hand movements; O. S., 20/25. Dense vitreous opacities, O. D., obscuring fundus details. Anterior chambers of moderate depth, angles narrow, partial peripheral anterior synechiae, O. U. Tension: O. D., 22; O. S., 30. Media clear; mild cupping, left disc. Glaucoma field, O. S. (Fig. 6). Tension O. S. remained elevated at 26 and 30 on 2% pilocarpine q. i. d., and further loss of field occurred. December, 1954: Cyclodiathermy, O. S., 8 punctures. April, 1958 (Final examination, 40 months after operation): vision: O. S., 20/30. Visual field unchanged since operation. Pilocarpine, 2%, O. S. q. i. d. has been needed to control tension. With medical treatment, tensions have varied between 12 and 24. Patient also taking acetazolamide, 250 mg., b. i. d. Corneal sensitivities normal, O. U.

CASE 8 (Fig. 7).—Man, age 65. Both eyes, chronic simple glaucoma (Fig. 7). March, 1953: First seen for routine examination with no eye complaints; diabetic. Vision: O. D., 20/20; O. S., 20/15. Tension: O. D., 27; O. S., 30. Glaucoma

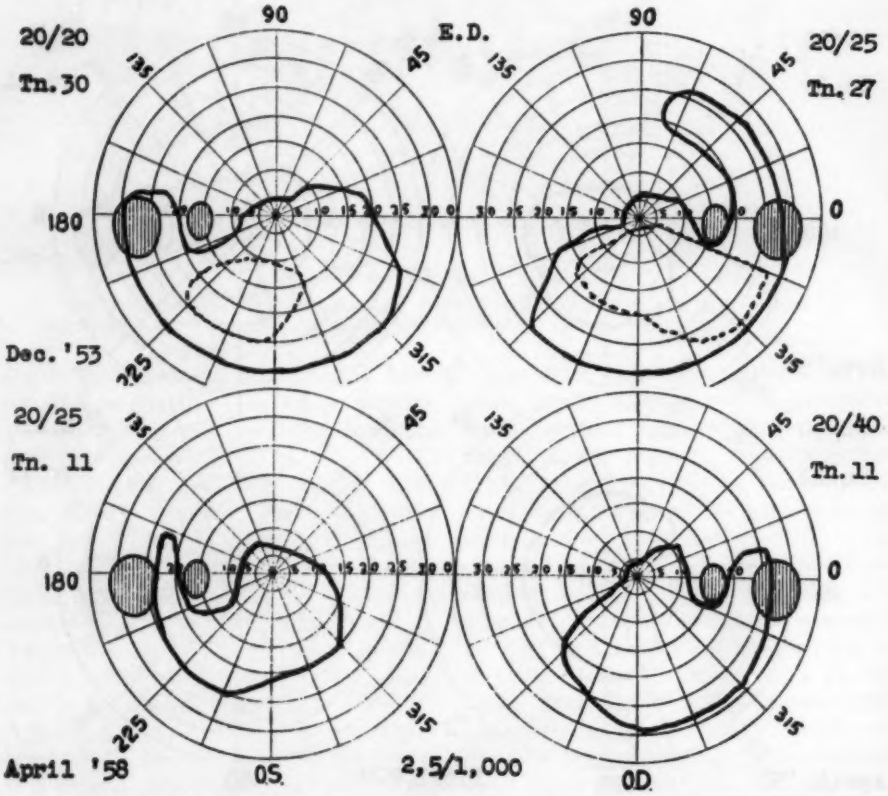

Fig. 7 (Case 8).—Vision, tension, and fields. Upper: at time of operation. Lower: 52 months after operation.

fields, O. U. Incipient senile cataract, O. U. Early senile macular degeneration, O. D. No cupping. Angles open, no goniosynechiae. January, 1954: Tensions intermittently above normal on miotics, including DFP, 0.1%. More loss of visual field, O. U. (Fig. 7). Slight decrease in vision owing to increase in lens opacities. Vision: O. D., 20/25; O. S., 20/20. Cyclodiathermy, 8 punctures, O. D.; 10 punctures, O. S. February, 1959 (Latest examination, 61 months postoperative): Lens changes slightly more advanced. Vision: O. D., 20/50; O. S., 20/25. Tension consistently between 12 and 19, O. U. During first two years after operation, 2% pilocarpine was needed to control tension; since then, probably not. Miotics were discontinued 54 months postoperatively, because they aggravated blurring of vision, owing to presence of cataracts. Tension remains between 12 and 19, O. U. In spite of normal tensions, there has been continued gradual contraction of visual fields, as is frequently seen in normotensive eyes after surgery. Fortunately, this has been so far confined mainly to the more peripheral portions of the fields. Corneal sensitivities diminished, O. U.

Results and Comments

The results can best be evaluated by considering separately the effects of treatment on tension, visual acuity, and fields (Table, Figs. 1-7) and by noting the incidence and nature of any complications.

1. *Tensions.*—Preoperatively, the tensions could not be controlled in any of the cases. Postoperatively, all tensions have been normal with or without medical treatment, for periods varying from 12 to 61 months. No significant changes in facility of aqueous outflow,‡ ocular rigidity,§ or gonioscopic appearance of the chamber angles were noted. Miotics were needed in 9 of the 13 eyes. In two of these eyes (Case 8), it later became possible to discontinue them. In another three eyes, miotics were given but were probably not necessary.

Pilocarpine was adequate for seven of the nine eyes requiring miotics; DFP was needed for the other two (Cases 5 and 6). Carbonic anhydrase inhibitors in addition to miotics were necessary to control the tension of one eye (O. D., Case 5). They were prescribed for three other patients (four eyes) as an added precaution, even though the tension of these eyes with miotics was always normal.

Only one eye required a second cyclodiathermy (O. D., Case 5). This has given good results during 19 months of observation. The fellow eye of the same patient was the only one in the series to show hypotension (less than 10 mm. Hg) of more than one or two days' duration. This eye remained soft for four weeks before returning to a normal level of tension. Postoperative observation suggested that the low tension in this buphthalmic eye could be attributed to filtration through the cyclodiathermy punctures, lasting four weeks, owing to the abnormally thin and stretched condition of this patient's sclera.

Tonometry has not been carried out on the operating table, but palpation of the globe at the end of the operation has generally revealed a soft eye. We have not experienced hypertension at operation or in the early postoperative period, as has been observed by some others. This may be due to the fact that the 1½ mm. electrode leads to some initial filtration in almost every procedure. The retrobulbar injection may also be a factor. It is our impression, however, that any filtration is of short duration and is not a factor in long-term control. Postoperatively, any suggestion of filtration on slit-lamp examination disappears within a short time. The facility of aqueous outflow remains at the preoperative level.

In this series, miotics were generally commenced within three to five days of operation, at a time when the tensions were

‡ Below normal in all eyes tested, pre- and postoperatively.

§ Ocular rigidities normal in all eyes, pre- and postoperatively.

normal in every case. This was done to assure the maintenance of normal intraocular pressure between the time of discharge from hospital and the first postoperative office visit and between subsequent office visits. It is not known whether this early postoperative use of miotics played a role in the favorable course which followed.

Topical steroids were given routinely for one week postoperatively to counteract any postoperative uveitis or tendency to posterior synechia formation. Neither of these were seen. It is also not known whether the early postoperative use of topical steroids beginning on the first postoperative day played any role in the favorable results.

2. *Visual Acuities.*—(*a*) Twelve Months Postoperative: The Table indicates that (1) preoperative vision was maintained in 10 of the 13 eyes; (2) in two eyes, the slow progression of lens opacities resulted in a decrease in vision of one line on the Snellen chart (20/80 to 20/100, O. S., Case 3; 20/25 to 20/30, O. D., Case 8); (3) in a third eye, a similar reduction of vision was noted (20/25 to 20/30, O. S., Case 7), but the reason was not apparent; (4) five other eyes with early cataracts showed no measurable loss of vision during the first year.

(*b*) Most Recent Examination (Twelve to Sixty-One Months Postoperatively: 1. Seven eyes retained their preoperative vision for periods of observation varying from 12 to 47 months (Table). 2. Only two eyes showed a reduction of more than one line on the Snellen chart, and both were due to slowly advancing cataracts (20/80 to 20/200, O. S., Case 3, after 19 months; 20/25 to 20/50, O. D., Case 8, after 61 months). 3. The fellow eyes of the same patients showed loss of vision of one line on the Snellen chart (20/200 to 20/300, O. D., Case 3; 20/20 to 20/25, O. S., Case 8). 4. Case 6, with vision of "counting fingers at 1 ft." in the temporal field of his only seeing eye, maintained this degree of sight for three years, before progression of his cataract reduced it to hand-movements.

In summary, no decrease in vision occurred that could be ascribed to the operative procedure. Visual loss in the patients with early cataracts was less than that usually seen. No eyes which did not have cataractous changes preoperatively developed them postoperatively.

3. *Visual Fields.*—In 11 out of 13 eyes (7 out of 8 patients) the visual fields maintained their preoperative level throughout the period of observation (Figs. 1 to 6).

Small regular, concentric fields, as seen in Figures 1, 2, 3, and 6, are sometimes retained for considerable periods even when the tension is not normalized.[1,2,11] Irregular concentric fields, such as those in Figures 4, 5, and 7, have a poorer prognosis. Operation may be followed by invasion of the fixation area or by complete loss of vision. And even after normalization of tension, field loss continues in 50% or more of cases.[1,2,11,12]

In the instance of Case 8 (Fig. 7), a slow but steady contraction of the field has continued over a postoperative period of 61 months, in spite of normal ocular tensions generally between 12 and 19 mm. Hg. Fortunately, the continued loss has been confined to the peripheral portions of the field and has taken place at a slower rate than observed preoperatively. While the long-term prognosis is uncertain, the operation appears to have been successful in prolonging this patient's period of useful vision.

4. *Complications.*—There were few complications. Six eyes of four patients showed varying degrees of corneal hypoesthesia (Cases 1, 3, 6, and 8). This was probably attributable to the operation (injury to sensory nerve supply to cornea), since in two unilateral cases the unoperated fellow eye showed normal corneal sensitivity. The complication could probably be prevented by avoiding the horizontal meridian. Also in these eyes, there was a mild reduction of tear formation as indi-

cated by the Schirmer test (7, 10, 10, and 12 mm. of Whatman No. 41 filter paper moistened after five minutes; normal 15 mm.). Two of the same patients (Cases 3 and 6) complained of burning and a sense of dryness in the eye operated on a few months postoperatively. The Schirmer test showed decreased tearing. The symptoms were readily controlled with instillations of 1% methyl cellulose.

Corneal sensitivities and the Schirmer test were normal in all the other eyes.

Early endothelial dystrophy, noted preoperatively in two cornea (Case 3), was not affected by the operation.

Summary and Conclusions

Thirteen glaucomatous eyes, with advanced field changes (isopter for 3/1,000 within 5 degrees of fixation point) in which the tensions could not be medically controlled, were treated by cyclodiathermy followed by a continuation of medical therapy.

Ten eyes had chronic simple glaucoma. Both eyes of one patient had juvenile glaucoma with hydrophthalmos. One eye with long-standing neglected high tension defied accurate classification.

In four patients the eye to be operated on was the only one with useful vision, vision in the fellow eye being hand-movements or less.

The operative technique was basically that of Castroviejo and consisted of 8 to 16 perforating diathermy applications through conjunctiva and sclera with a 1½ mm. electrode, 6 mm. from the limbus, evenly distributed around the circumference, each application being for 10 seconds.

Length of postoperative observation was from 12 to 61 months, the average being 30 months.

Safe levels of normal tension were achieved in all eyes by the combined approach.

In twelve eyes, one cyclodiathermy procedure sufficed; in one eye, a second was needed.

Miotics were required postoperatively in 9 of the 13 eyes. In two of these eyes it later became possible to discontinue them. In another three eyes, they were also used but were probably not needed.

No reduction in vision resulted from the operation or from any postoperative abnormalities of intraocular pressure.

Lens opacification was not accelerated by the operation. Acquired lens changes, noted preoperatively in seven eyes, progressed slightly in five eyes and not at all in two eyes. The rate of progression was not greater than would have been expected had no operation been done. None of six eyes having clear lenses before operation developed lens opacities.

No significant changes in facility of aqueous outflow or gonioscopic appearance of the angles were induced by the cyclodiathermy.

The tension-lowering effect of the operation was not related to any changes in ocular rigidity, which was normal in all eyes both pre- and postoperatively.

Corneal hypoesthesia was noted postoperatively in six eyes. This can possibly be prevented by avoiding the horizontal meridian at the time of operation.

While serious complications can result from overenthusiastic application of cyclodiathermy, these are rare with the technique used here. The commonest complication met will be that of insufficient effect, but in such a case the procedure can be repeated with an almost equally good chance of success. Properly performed, this operation has a wide margin of safety. This is an advantage, because the greater dangers inherent in other operations are conducive to procrastination.

In cases such as these, cyclodiathermy is obviously not the final answer and may still leave much to be desired. But when the field changes are so advanced, can any perfect answer be anticipated, other than earlier diagnosis and/or more effective treatment in the earlier stages of the disease?

As is so often the case, so also here: the best approach for any surgeon is the one

that gives the best results in *his* hands. Those who obtain results as good or better than these by other methods should not change. For those, however, who are not satisfied with their present results, this combination of cyclodiathermy and continued medical therapy can be recommended as a technically simple, reasonably safe, and relatively successful method of approach to a difficult problem.

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The Prognosis in Temporal Arteritis

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The clinical picture of temporal arteritis was first described [1] by an English surgeon, Jonathan Hutchinson, in 1889. He told of an elderly "gentlemen's servant" who complained of "red streaks on his head which were painful and prevented his wearing his hat. The red streaks proved, on examination, to be his temporal arteries which on both sides were found to be inflamed and swollen." Temporal arteritis was not defined as a disease entity until 1932, by Horton, Magath, and Brown.[2] Since then over 300 cases have been reported in the literature in an impressive number of articles.

Temporal arteritis is recognized as a relatively uncommon disease of obscure etiology, occurring in people from 52 to 84 years of age. Usually it is characterized by a persistent, low-grade fever and a severe headache, most intense in the region of the prominent, tender temporal arteries. Many patients complain of pain on chewing. Vision is seriously diminished in about 50% of the cases due to ischemic optic neuropathy or occlusion of the central retinal artery. Biopsy of an involved artery typically shows a granulomatous arteritis with giant cells of the Langhans type and a narrowed lumen often occluded by an organized thrombus.

Despite evidence that there is a systemic disease of which temporal arteritis is but one manifestation, little information is available indicating the ultimate prognosis for life or for later involvement of the intracranial arteries. In a review of the total of 48 cases reported to date in 1948, Crosby and Wadsworth [3] estimated that the mortality was 12.5%, but this was necessarily based on a short term follow-up for most of the cases.

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The present paper is an attempt to determine the prognosis for life and to evaluate the effect of steroid therapy on 32 cases of temporal arteritis seen at the Massachusetts Eye and Ear Infirmary and at the Massachusetts General Hospital. The individual cases are listed in the accompanying Table. The minimum follow-up period was 15 months. Ten of the thirty-two patients were followed for from 5 to 12 years.

In this series of 32 patients the basis for the diagnosis of temporal arteritis was fever, pain, tenderness, and swelling in the region of the temporal arteries, with or without visual symptoms. In 23 of the 32 cases a biopsy was done and found to be positive.

Ocular Findings

Eleven of the thirty-two patients, 34%, became blind in both eyes as a result of the disease.

Seven patients, 21%, became blind in one eye as a result of the disease. Vision was seriously impaired in the second eye of one of these patients. Six lost no vision in the second eye.

Two patients, 6%, had moderate visual damage in both eyes.

Of the 32 patients, 2 showed transient paresis of the extraocular muscles.

Three patients had altitudinal field defects. One patient had a nasal field defect which disappeared under steroid therapy.

Twelve patients had no eye symptoms.

Mortality and Duration

Eleven of the thirty-two patients have died. Three of them died as a result of cerebrovascular accident; one at 4, another at 10, and the third at 12 years after the

Summary of Case Data *

	Age at Onset, Yr.	Biopsy	Vision After Cessation Temporal Arteritis		Involvement Extraoc. Ms.	Visual Field Defect	Steroids Used	Duration of Disease, Mo.	Recurrence	Length of Follow-Up, Yr.	Present Status	Cause of Death
			O. D.	O. S.								
1	73	+	20/40	20/200	Yes	Upper O. D.	Yes	3	None	2	Living	
2	73	+	Blind	Blind	No	None	No	4	None	8	Dead	Chronic myocarditis
3	74	+	Blind	Blind	No	None	No	3	None	12½	Dead	Cerebrovascular accident
4	76	+	Blind	Blind	No	None	No	3	None	3½	Living	
5	77	+	Blind	Blind	No	None	Yes	2	None	5	Living	
6	74	+	20/30	20/30	No	Lower O. S.	Yes	3	None	2	Living	
7	52	+	Blind	Blind	No	None	Yes	5	None	2	Living	
8	60	+	—	—	No	None	No	11	None	10	Dead	Cerebrovascular accident
9	71	+	—	Blind	No	None	Yes	11	None	2	Dead	Coronary thrombosis
10	69	+	—	—	No	None	No	3	None	1½	?	
11	68	+	—	—	No	None	No	4	None	10	Living	
12	74	+	—	—	No	None	No	11	None	6	Dead	Cardiac decomp. & hyp. ht. dis.
13	73	+	—	—	No	None	No	8	None	1½	Dead	Acute left ventricular failure
14	82	+	Blind	Blind	No	None	Yes	6	None	1½	Living	
15	75	+	—	—	No	None	Yes	2	None	2½	Living	
16	68	+	Blind	20/30	No	Upper O. S.	Yes	3	None	4½	Living	
17	71	+	—	—	No	None	No	2	None	8	Dead	Pulmonary embolism
18	58	+	—	—	No	None	Yes	3	None	3½	Living	
19	78	+	Blind	Blind	No	None	No	6	None	3	Living	
20	73	+	20/20	Blind	No	Transient	Yes	3	None	3½	Dead	Coronary thrombosis
21	79	+	Blind	Blind	No	None	No	12	None	2	Dead	Art. sclerotic heart disease
22	84	+	Blind	Blind	Yes	None	Yes	2	None	2	Living	
23	76	+	—	—	No	None	No	8	None	5	Living	
24	72	None	Blind	Blind	No	None	No	3	None	4	Dead	Cerebrovascular accident
25	71	None	—	—	No	None	Yes	3	None	6	Living	
26	66	None	Blind	Blind	No	None	No	6	None	7	Dead	Art. sclerotic heart disease
27	65	None	Blind	20/20	No	None	Yes	6	None	3	Living	
28	71	None	Blind	20/20	No	None	Yes	5	None	4	Living	
29	64	None	—	—	No	None	Yes	3	None	3½	Living	
30	71	None	Blind	—	No	None	Yes	2	None	3½	Living	
31	67	None	—	—	No	None	Yes	3	None	2	Living	
32	82	None	—	Blind	No	None	Yes	3	None	3½	Living	

* + indicates biopsy of temporal arteritis was positive; —, vision not affected by temporal arteritis.

onset of temporal arteritis. Two died from coronary thrombosis at 2 and 3½ years after the onset of temporal arteritis, and five from chronic heart disease at 1½, 2, 6, 7, and 8 years after the onset. One died of a pulmonary embolism 8 years after the onset. None of the series died during the active phase of the disease, and in no case was death attributed to arteritis.

The duration of temporal arteritis in this series varied from 2 to 12 months, with an average duration of 4½ months. None of the 32 patients had a recurrence after the active phase of the disease disappeared.

Steroid Therapy

The effect of steroid therapy may be inferred in the present series by a comparison of 14 patients who received no steroid therapy with 18 patients who did receive it. Of the former, seven became completely blind in both eyes due to temporal arteritis. The remaining seven had no visual damage.

Of the 18 patients treated with steroids, 4 became blind in both eyes, 7 became blind in one eye, 2 who had transient visual disturbance in both eyes recovered useful vision, and 5 had no visual symptoms at all. Of these 15 blind eyes, 11 were blind before steroid therapy was started. Of the seven patients who became blind in one eye, six did not lose vision in the second eye and one retained 20/30 vision but had a permanent altitudinal field loss.

Thus, it appears that steroids have a salutary effect, but vision may be lost despite and during steroid therapy. Steroid therapy, however, brought about dramatic relief from pain.

Comment

The high instance of ocular involvement in temporal arteritis has been stressed many times in the literature, particularly by Wagener and Hollenhorst,[4] in 1958. Forty-four per cent of their series developed seriously impaired vision as compared with fifty-five per cent of the group reported in this paper.

Birkhead and Wagener,[5] in 1957, reported the beneficial effect of steroid therapy in the treatment of a series of 55 temporal arteritis patients. Our cases also suggested a beneficial effect from steroids but not to so great an extent.

In the literature at least seven autopsies [6-11] have been reported on patients who died during the active phase of temporal arteritis. All of these autopsies showed a similar granulomatous arteritis in other areas of the body. Other arteries involved varied from case to case but included the aorta, radial, subclavian, femoral, renal, coronary, mesenteric, carotid, vertebral, celiac, iliac, popliteal, ophthalmic, and central retinal. In spite of this finding of widespread arteritis, it was not always clear that arteritis was the cause of death. It is noteworthy that no deaths in the series of 32 patients reported in this paper were attributed to arteritis and that Wagener and Hollenhorst,[4] in 1958, mentioned no deaths in their series of 122 cases. Also the present series gave no evidence that intracranial vascular disease was associated with temporal arteritis.

Among unusual complications, Kendall [12] reported one case of deafness developing during temporal arteritis. He also reported that another patient developed an extensive area of necrosis of the scalp and also necrosis of the nasal septum with perforation of the cartilage. Allen, Barker, and Hines [13] reported that one patient developed a hemiplegia and another had an acute myocardial infarct during active temporal arteritis and while receiving steroid therapy. Both of these patients recovered. The same authors also cited one instance of sudden, complete, and permanent deafness developing during the course of temporal arteritis. No such complications occurred in the present series.

Summary

A follow-up of from 15 months to 12 years is herein reported on 32 patients with temporal arteritis. The duration of the disease varied from 2 to 12 months. There was no instance of recurrence. Of 11 pa-

tients who have died, 3 died of cerebrovascular accident, 7 of heart disease, and 1 from pulmonary embolism, all unrelated to temporal arteritis. Eighteen of the series became blind in one or both eyes. Steroid therapy in this series was very effective in relieving pain and in some cases appeared to lessen visual damage.

266 Beacon St. (16).

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Simultaneous Occurrence of Primary Malignant Melanomas of the Eye and the Skin

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The simultaneous occurrence of primary malignant melanomas of the skin and choroid has not been previously reported. Also, the literature contains only five references to familial ocular melanomas. Therefore, the following case merits attention, for it illustrates both of these unusual circumstances.

Report of a Case

The patient is a 72-year-old white married housewife from West Virginia who was admitted to the surgical service of the National Cancer Institute on June 5, 1957. Six years prior to admission she first noted a flat brown spot near the lateral canthus of the right eye. The lesion was repeatedly treated by electrocautery in the following years. Initially she received two treatments per year; then, owing to progressive enlargement, four times yearly and eventually monthly. Nine months prior to admission she first observed a discrete nodule forming at the lateral canthus at the site of the original lesion, and three months thereafter she became aware of a progressive brown discoloration of the eyeball itself. The skin nodule was removed at a hospital in Beckley, W. Va., and a diagnosis of malignant melanoma was made (Fig. 1).

It is of particular interest that the patient's 86-year-old brother had his right eye enucleated nine years ago for malignant choroidal melanoma. The tumor is reported to have consisted of "spindle cells, Type A or B."[1] No other members of the family

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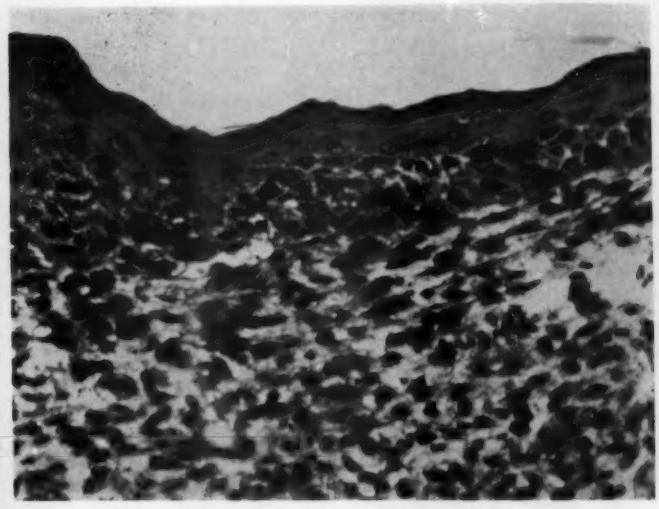

Fig. 1.—Primary cutaneous malignant melanoma which developed lateral and slightly inferior to the lateral canthus of the right eye. The tumor is composed of small oval and spindle-shaped cells. Hematoxylin and eosin; reduced about 10% from mag. × 310.

Fig. 2.—The patient in June, 1957, shortly before right orbital exenteration. There is a zone of black pigmentation of the skin at the lateral canthus, and dark pigmentation extends along the upper and lower eyelid. A small scar at the inferior margin of the pigmented zone is the site from which the primary cutaneous melanoma was removed five weeks previously. A small raised nodule can be seen in the upper lid, and there are several white cilia growing at the site of this nodule. The degree of melanosis of the bulbar conjunctiva is not well illustrated in this photograph.

are known to have had either cutaneous or ocular melanomas. There was no consanguinity of their parents. The patient has had eight children, five of whom are living and range in age from 33 to 48. None has known ocular abnormalities.

On admission the pertinent physical findings were those related to the right eye and periorbital skin (Fig. 2). A triangular zone of skin adjacent to the lateral canthus was intensely pigmented and was thickened, wrinkled, and indurated. This zone extended from its apex, about 4 cm. from the canthus, to the temporal lid margins, which were also pigmented. There was a separate 3 mm. nodule near the margin of the upper lid, and several white lashes extended from it. Patches of pigmentation were present on the temporal palpebral conjunctiva. Melanosis of the bulbar conjunctiva extended from the lateral canthus to the limbus. There were irregular areas of pigmentation on the cheek and a small scar at the site of previous excision of the melanoma, just inferior to the lateral canthus.

Results of ophthalmological examinations were as follows: Vision corrected to 20/25 bilaterally. There were no abnormalities of the extraocular muscles, corneal sensitivity, pupillary reaction, anterior chamber angle, and intraocular tension. There was no heterochromia. On biomicroscopy, the conjunctival melanosis of the involved eye showed no evidence of scleral extension. No abnormal iris thickening or pigmentation was present. Incipient cuneiform lenticular changes were seen bilaterally. On funduscopic examination a circumscribed area about 1 d. d. in size was noted just inferior to the macula. It appeared slate gray, round, and flat and produced no field defect with the 1/1,000 white test object. Clinically this lesion had the characteristics of a benign choroidal melanoma. The remainder of the fundus, including the disc, the macula, and the periphery of the retina, was normal in appearance. Both fundi were equally pigmented. The left eye showed no pathological changes.

Laboratory studies, including chest x-ray, skull x-rays with orbital views, urine melanin test, routine blood studies, and electroencephalogram were all normal.

It was decided that the skin lesion should be widely resected, including an orbital exenteration. The operation was performed by Dr. Robert R. Smith on June 19, 1957. The patient had an uneventful postoperative course and was last seen 17 months after discharge, at which time examination showed no recurrent or metastatic melanoma.

Pathological Examination.—A histological section of the nodule removed before the patient was admitted to the Clinical Center showed a malignant melanoma of the skin (Fig. 1). This tumor was approximately 1 cm. in diameter and was composed of round and spindle-shaped melanoma cells, only a few of which contained melanin.

The operative specimen of June 19, 1957, consisted of the right eye, periorbital tissue, upper and lower eyelids, and a wide margin of skin lateral and inferior to the lateral canthus which contained the skin lesions described clinically. Dark pigmentation was present in the conjunctiva, the

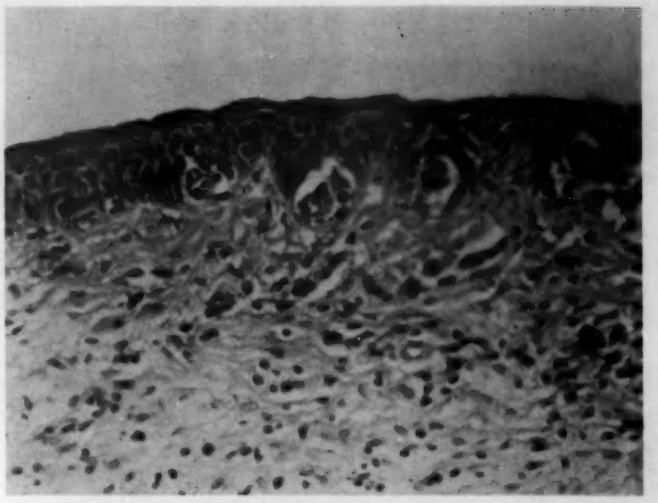

Fig. 3.—Section of darkly pigmented skin adjacent to lateral canthus showing junctional nevus. Hematoxylin and eosin; reduced about 10% from mag. × 310.

skin adjacent to the lateral canthus, and along the upper and lower eyelids. The surrounding skin appeared roughened and atrophic. The slightly raised nodule at the margin of the upper lid which contained white cilia was covered by thin shiny epidermis.

Histological sections of the skin showed a small number of residual melanoma cells near the cutaneous scar where the primary cutaneous melanoma had been excised. Junctional nevus was seen in the epidermis lateral and inferior to the lateral canthus. Junctional nevus was encountered in both darkly pigmented and normally pigmented parts of the skin and also appeared in sections of the upper and lower eyelids and palpebral conjunctiva. This irregular but widespread lesion is illustrated in Figures 3 and 4. Not all of the dark discoloration noted in the skin was due to pigment in nevus cells, since in many parts of the skin there were numerous

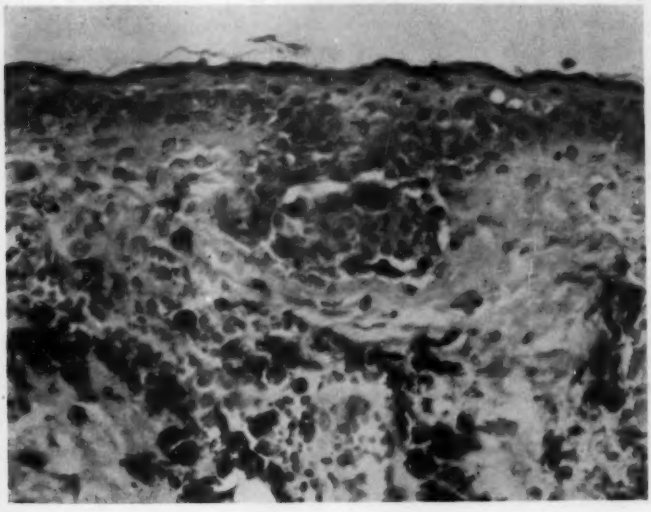

Fig. 4.—Section of skin below lateral half of lower eyelid. There is a group of heavily pigmented nevus cells in the epidermis. Numerous pigmented macrophages are present in the dermis. Hematoxylin and eosin; reduced about 10% from mag. × 310.

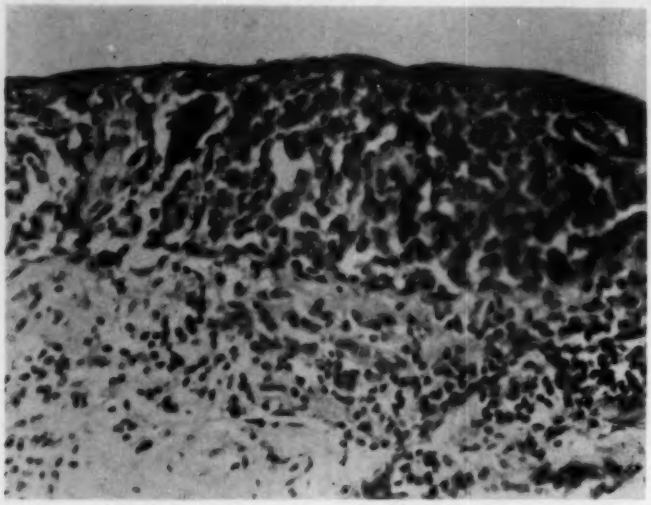

Fig. 5. — Small melanoma in the upper lid. The melanoma cells extend nearly to the surface of the epidermis. There is a lymphocytic infiltrate in the adjacent dermal connective tissue. Hematoxylin and eosin; reduced about 10% from mag. × 310.

melanin-containing macrophages in the dermis (Fig. 4). The skin at the margins of the surgically resected specimen showed severe atrophy and senile elastosis.

The discrete nodule in the upper eyelid proved histologically to be a small superficial malignant melanoma. It consisted of polyhedral and spindle-shaped melanoma cells with dark cytoplasm and irregular nuclei which replaced the epidermis and superficially infiltrated the adjacent dermis (Fig. 5). Some of the cells contained melanin. There was junctional nevus in the epidermis of the eyelid on each side of this small melanoma. No pigmented cells or melanoma were seen in sections of the periorbital fat, extraocular muscles, and optic nerve.

The eye and bulbar conjunctiva were separated from the operative specimen and were fixed in Bouin's solution, then opened in the horizontal plane. The vitreous was clear, and the inner membrane exhibited only a faint grayish area below the region of the macula. The eye was embedded in celloidin and sectioned serially. Selected sections were stained with hematoxylin and eosin and Wilder reticulin stain, and bleached sections were made by Lillie's modification of the performic acid technique.

There were areas of precancerous melanosis in the conjunctival epithelium. These

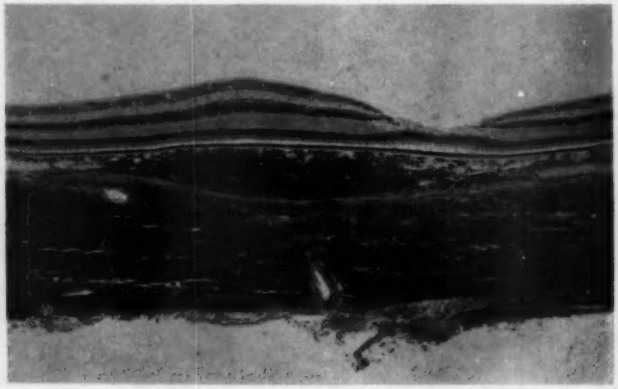

Fig. 6.—Section of eye through the macula. The choroidal melanoma is seen to lie entirely within the choroid; the overlying retina is undisturbed. Relationship of this tumor to a ciliary nerve is not demonstrated in the section. Hematoxylin and eosin; reduced about 35% from mag. × 50.

consisted of pigment-bearing cells within the epithelial layer, hydropic changes of the basal cells, moderate disarrangement and proliferation of the epithelium, and mononuclear infiltration of the subepithelial layers. The pigmented cells in the conjunctival epithelium did not exhibit marked anaplasia, and no mitotic figures were seen.

The anterior chamber had normal depth and an open angle. The iris and ciliary body appeared histologically normal. The lens exhibited signs of early posterior cortical cataract. The vitreous was free of cells and abnormal deposits. The retina had normal architecture except for a moderate number of Blessig cysts near the ora serrata. The pigment epithelium was uniformly and densely pigmented and slightly elevated by drusen of Bruch's membrane at several sites.

Study of sections through the slate-gray area below the macula showed choroidal melanoma (Fig. 6). This grossly circular lesion was 2 mm. in diameter and 0.3 mm.

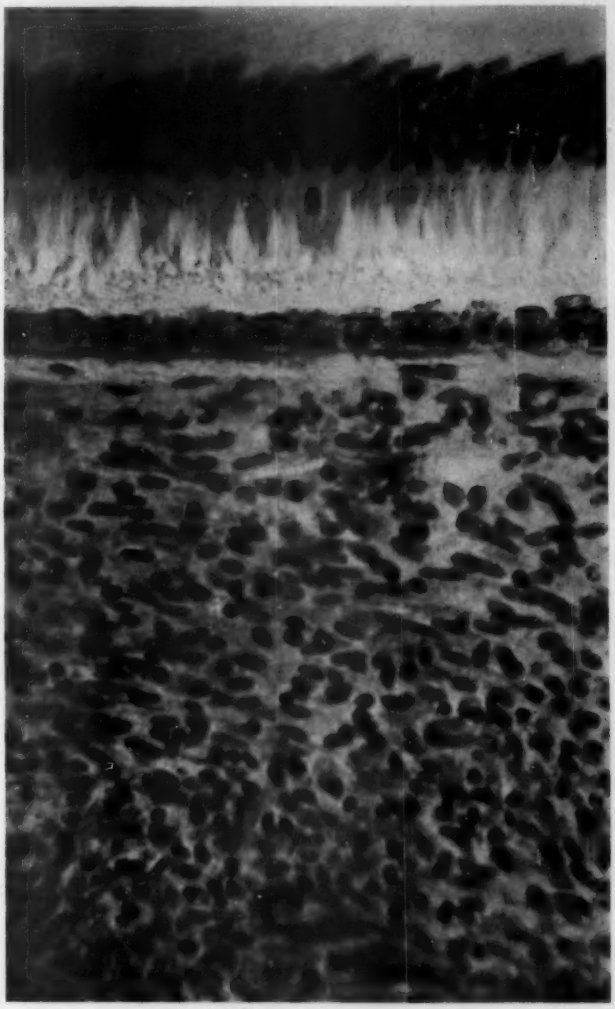

Fig. 7.—Higher magnification of the choroidal melanoma shown in Figure 6. Performic acid bleach, hematoxylin and eosin; × 500.

in thickness. The overlying retina was not visibly elevated and was histologically normal. Bruch's membrane was intact in every section, as was the choriocapillaris. In some sections, the inner layers of the sclera were separated by tumor cells and there was some thinning of the scleral coat but no extension into its outer layers. A ciliary nerve extended to one border of the tumor, and at this site there was proliferation of Schwann sheath cells.

The melanoma consisted of heavily pigmented cells centrally and somewhat less pigmented cells in the periphery. Small choroidal vessels were present throughout the tumor, but tumor cells did not invade them. In preparations stained according to the Wilder technique, there was a prominent reticulin fiber network. Bleached sections (Fig. 7) showed spindle cells with fine reticular pattern in the nucleus and poorly defined nucleoli—these cells comprised the bulk of the tumor and were Type A according to the Callender classification.[2] Other spindle-shaped cells, Callender Type B, had darker staining nuclear material and sharply outlined nucleoli.* Choroidal melanocytes were scattered throughout the tumor.

* Sections of the tumor were also examined by Dr. Lorenz Zimmerman, of the Armed Forces Institute of Pathology, who concurred in the diagnosis of early malignant melanoma with spindle cells, Types A and B.

A separate focus of lightly pigmented cells was located in the outer portion of the choroid nasal to the optic nerve and thus completely independent of the melanoma described above (Fig. 8). This was composed of smaller cells with darkly stained nuclei and ill-defined cell membranes; it was a more loosely arranged cellular group with a fine reticulin network. This collection of pigment cells was considered a benign lesion.

Comment

The diagnosis of malignancy of the paramacular choroidal tumor has been made upon the arrangement and characteristics of the component cells. The distinction between malignant and potentially malignant tumors may become an academic argument. One of three consultants was unwilling to call the lesion malignant, differing in his opinion on the interpretation of Type B spindle cells. However, the cells described are the same as those found in larger, distinctly invasive tumors.

The small size of this paramacular choroidal melanoma which clinically fulfilled the specifications of a benign lesion makes it perhaps the earliest choroidal melanoma to be clinically and histologically described. Since the report by Fuchs [3] of a melanoma completely confined to the choroid without involvement of the overlying retina, a number of others have been reported. The

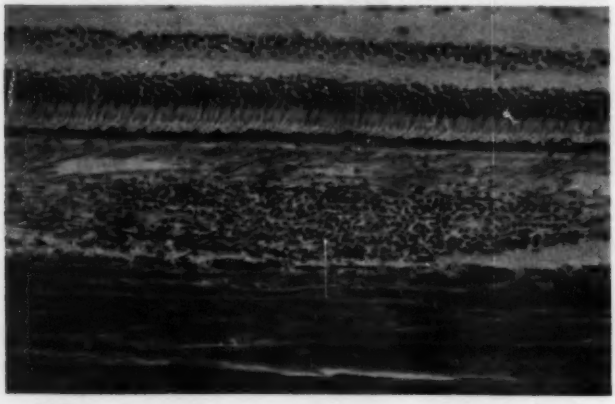

Fig. 8.—Second focus of pigmented cells located nasal to the optic disc and in the outermost layers of the choroid. Hematoxylin and eosin; reduced about 35% from mag. × 270.

earlier literature has been reviewed by Schappert-Kimmyser and Mulock Houwer.[4] Among more recent cases is one reported by Wilder.[5] Sparing of the choriocapillaris with normal appearance of Bruch's membrane and the overlying retina account for the absence of visual field defect.

The choroidal melanoma and the cutaneous melanomas are considered independent, primary tumors occurring simultaneously in this patient. Histologically there is precancerous melanosis of the bulbar and palpebral conjunctiva associated with widespread active junctional nevus in the periocular skin. The cutaneous melanoma lateral to the eye is thought to be a primary lesion because there is a definite junctional component in the epidermis overlying the tumor. For this same reason the superficial melanoma in the upper eyelid is interpreted as being primary at that site. It would, moreover, be unlikely that the small choroidal melanoma could have preceded the skin lesions whose development had been observed clinically for five years. Thus, there is no evidence to favor the theoretical interpretation that the cutaneous lesions represent metastatic tumor deposits from the lesion in the choroid.

There is good evidence that the choroidal tumor cells are not metastatic from the skin or invaders from the epibulbar tissue. Choroidal melanocytes were present amid the spindle-cell choroidal tumor—suggesting that the choroidal tumor occurred at the site of these precursors. Also, proliferation of Schwannian cells was observed around a ciliary nerve at the border of the tumor. It is this abundance of precursor cells which most significantly demonstrated the primary choroidal origin of the tumor. The second small choroidal lesion nasal to the optic disc was composed of cells unlike those of either the skin melanoma or the paramacular choroidal melanoma. This smaller choroidal lesion had no demonstrable relation to a nerve or to surrounding melanocytes, and was considered a benign proliferation of pigment cells. Even from simply a statistical viewpoint metastasis to the choroid would appear to be very unlikely. Jensen,[6] in reviewing the literature, found only 15 authenticated cases of metastases of melanoma to the choroid. It may be, however, that were the eyes of patients dying from widespread metastatic melanoma systematically examined a higher incidence of these metastases would be found. The possibility of local tumor spread from the skin to the choroid is even less likely. Although there was precancerous melanosis of the bulbar conjunctiva, no melanoma cells were found in the periorbital tissues or sclera.

The histological appearance of the ocular lesions in this patient is different from melanosis oculi, which bears a clinical resemblance and which is associated with choroidal melanoma in a variously estimated 10% to 29% of cases.[7] Melanosis oculi is a congenital, usually unilateral increase in the pigment of all the pigment cells throughout the uvea as well as of the conjunctiva, lids, and even the extraocular muscles. It is distinguished from precancerous melanosis by its congenital occurrence, the presence of pigment almost exclusively in the subconjunctival tissues rather than the conjunctival epithelial cells, and involvement of the uveal tract. When combined with ipsilateral dermal pigmentation of the lids and face the syndrome is called oculodermal melanocytosis,[8] synonymous with the older term, nevus of Ota. Almost all cases of oculodermal melanocytosis have been described in Orientals. Although melanosis oculi and oculodermal melanocytosis might both be mentioned in comparison to the case presented, the histological distinctions are great. No tenable explanation can be offered to explain the proximity of skin and choroidal melanomas in this case.

The patient's brother had a primary choroidal melanoma of the spindle-cell variety. The familial occurrence of ocular melanomas has been reported five times previously. Silcock[9] reported a 20-year-old woman with choroidal melanoma whose

mother and maternal grandfather also had the tumor. Pfingst [10] reported it in two brothers, and Reese [11] has seen two sisters with melanomas of the ciliary body. Irvine [12] recently reported a case of malignant melanoma of the bulbar conjunctiva in a patient whose sister had a choroidal melanoma. The largest series is that of Davenport,[13] who reported five definitely proven and two possible choroidal melanomas in three generations of the same family.

Summary

A case with simultaneously occurring cutaneous and ocular melanomas is reported. The conjunctiva exhibited precancerous melanosis. Separate origins of these melanomas are diagnosed.

The patient's brother also had a choroidal melanoma. The rarity of familial occurrence is indicated.

Clinical examination of the patient's paramacular choroidal melanoma was compatible with a benign lesion; histologically the overlying retina, Bruch's membrane, and the choriocapillaris were intact.

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Irradiance Thresholds for Chorioretinal Lesions

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Considerable information is now available concerning chorioretinal burns produced by atomic flash.[1-4] The purpose of the present research was to determine the threshold conditions for the production of such lesions and the course of healing in such a threshold burn. Since the ocular media transmit a relatively narrow spectral band, the source of energy used is not important, as long as its spectral emission covers the range from 0.3μ to 1.3μ (Fig. 1). However, since species may be an important factor and since human volunteers are not readily available, it was necessary to use several mammalian species in order to establish a basis for generalization to the human eye.

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The Department of Radiation Biology, University of Rochester School of Medicine and Dentistry.

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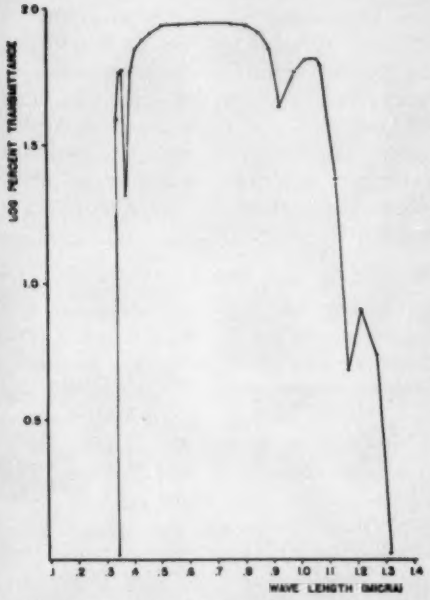

Fig. 1.—The spectral transmittance of the ocular media as measured in an excised steer eye, corrected for axial length to approximate the transmittance of the rabbit (or human) eye.

Apparatus

The light source used in this study was a U. S. Army searchlight, 24 in., Model 1942. The light from the carbon arc is focused by a reflector into a fairly intense beam with uniform flux-density within about 5 mm. of the center of the beam. A graduated series of circular apertures (artificial pupils) could be placed in the center of the beam to control the intensity of retinal irradiance. Exposure time could be varied from 40 msec. upwards by means of a shutter.

Procedure

Adult pigmented rabbits, cats, and guinea pigs were used. The pupils were dilated with atropine and the animals lightly anesthetized with pentobarbital (Nembutal). The animal was held with its eye about 3 mm. from the aperture, the pupil approximately centered on the beam. An exposure was made at an exposure time well below the expected threshold and the fundus examined with an ophthalmoscope. A threshold lesion appears as a sharply circumscribed translucent whitish area, apparently raised above the fundus. If no lesion was found, another exposure was made at a slightly longer exposure time and the fundus again examined. This process was repeated until a visible lesion was produced. The threshold was taken as midway between the last two exposure times

used. With the cats, it was sometimes necessary to hold the nictitating membrane out of the way with forceps while making the exposures. There is a slight possibility that a given area of retina may have received more than one exposure. The data would then be in error to the extent that such exposures are cumulative.

Calibration

The source used in the sudy had been previously calibrated, so that the flux passing through the aperture was known. In order to obtain retinal irradiance, however, two additional factors must be known: the distribution of flux in the retinal image and the absorption by the ocular media.

In order to determine the first of these factors, an artificial rabbit eye was constructed, consisting of an uncorrected, 12 mm. focal length lens in a holder which permitted a piece of photographic film to be positioned in the focal plane. By using the combinations of aperture and exposure time which had produced threshold lesions in the rabbit eye, a series of photographs was obtained, having nearly identical densities. Since the exposure times were precisely known and the reciprocity rule could be assumed over the range of exposure times used (0.04 to 0.8 seconds), the relative irradiances from the different apertures could be readily calculated. Unfortunately, it proved impossible to obtain comparison photographs at known irradiances, so that absolute irradiance could not be found by this means.

By placing the artificial rabbit eye in the beam and with use of a small Thermistor as an energy-sensing device, it was possible to obtain absolute measures of the irradiance in the "ocular" images with use of the different apertures. Although this method is less reliable than the photographic calibration, it was possible to use the relative scale obtained from the photographs to smooth out the irregularities in the absolute scale derived from Thermistor measurements and so obtain a fairly accurate final calibration.

Since the calibration was performed with a glass lens in place of the eye, it was necessary to know the spectral transmittance of the glass and of the ocular media in order to compute retinal irradiance from calibrated irradiance. The transmittance of the glass is readily available. The transmittance of the ocular media was measured in an excised steer eye.

The detailed procedure by which a steer eye may be prepared for such measurements has been described elsewhere.[5] In brief, the eye was placed in the beam of a Perkin-Elmer Universal Monochromator and the transmitted light measured by a lead sulfide cell in an integrating sphere. The output was measured as a function of wave length with and without the eye in the system, and the difference between the two curves was used to compute transmittance. No correction was made for reflection, and the opening in the sclera through which the transmitted light was recorded was large enough to include over 90% of the scattered light, as well as the directly transmitted light. The obtained transmittance curve is shown in Figure 1. Since the eye transmits about three-fourths the energy transmitted by the glass lens, the calibrated irradiance figures were multiplied by this factor to find retinal irradiance.

Results

The threshold values for irradiance and exposure time are shown in Figure 2. The points for the rabbit and cat eye have been plotted directly; those for the guinea pig have been corrected for the difference in focal length of the eye. The resulting curve is almost certainly a dual function. The portion of the curve to the right of 2 cal. per square centimeter per second is a straight line of Slope -1, indicating that the radiant exposure necessary to produce a lesion is constant and lies between 0.5 and 1.5 cal. per square centimeter. To the left of this value, the curve rapidly ap-

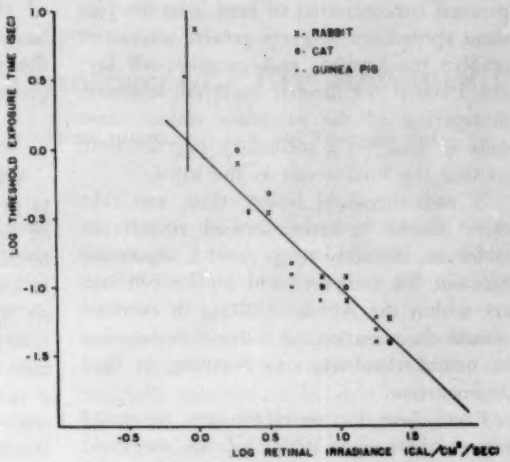

Fig. 2.—Exposure times required to produce a threshold retinal lesion as a function of retinal irradiance. The line of Slope —1 represents a radiant exposure of 1.0 cal. per square centimeter. At irradiance less than 0.7 cal. per square centimeter per second, retinal lesions could not be produced at any exposure time through 10 seconds.

proaches a vertical asymptote, indicating that a certain minimal level of irradiance is necessary before any exposure time will be effective. Apparently an equilibrium is established in little more than 10 seconds, in which heat is being removed by the blood supply at the same rate it is being absorbed.

Since the human blink reflex occurs with a latency of about 0.1 second, lesions would probably not occur with a retinal irradiance less than 4 cal. per square centimeter per second.

Histological Data

The animals were killed at increasing intervals and the eyes removed for histological examination. The data consisted of sections from 14 rabbit eyes and 2 guinea pig eyes, excised at periods from 5 minutes to 36 days post trauma.

No differences were found between the lesions in rabbits and guinea pigs or as a function of the intensity of irradiance. It should be reemphasized that all lesions were near threshold.

Immediately post trauma (5-30 minutes), the lesions consisted of intrusions of fluid, probably serum, into the sclera, choroid, and retina. The commonest appearance was of an intrusion between the receptor- and bipolar-cell layers of the retina. From 30 minutes to about 4 days post trauma, the fluid intrusions gradually coagulated and shrank. From 5 to 36 days there is apparently a gradual resorption of the clot.

At about seven days post trauma, we find the first appearance of retinal necrosis. This is not an inevitable result of a threshold lesion, as indicated by the fact that some lesions showed no such necrosis at several weeks post trauma and, where the necrosis was found, it was only in the central portion of the lesion.

Assuming that the intensity of irradiance was greatest at the center of a lesion, we can establish a sequence of effects with increasing intensity. The bare minimum would appear to be an intrusion of fluid within the retina or between the retina and choroid. The latter type of lesion produces a small, uncomplicated retinal detachment which shows a tendency to reattach as healing progesses. Where the intrusion is between the receptor- and bipolar-cell layers, as is more often the case in these subjects, functional loss should be permanent.

A slight increase of intensity causes a destruction of retinal elements. The pigment epithelium and receptor cells are the first to be destroyed, probably because the

greatest concentration of heat is in the pigment epithelium. Slightly greater intensities involve the bipolar- and ganglion-cell layers. Even if not directly involved, however, destruction of the receptors causes these cells to undergo a secondary degeneration, so that the final result is the same.

A near-threshold lesion, then, can take three forms: a circumscribed retinal detachment, probably temporary; a separation between the receptor- and bipolar-cell layers within the retina, resulting in eventual retinal degeneration, or a direct destruction of neural elements, also resulting in final degeneration.

From these data on rabbit eyes, we would expect that about 95% of all threshold lesions would fall into the latter two categories, resulting in permanent visual scotomata.

Comment

Owing to the peculiar laws of optics, the retinal irradiance from an extended source does not vary with distance, except as a function of absorption by intervening media. Aside from such absorption, retinal irradiance is a function of pupil diameter and the surface brightness of the source.

In the case of an atomic flash, the greatest probability of retinal damage would be created by a flash directly overhead at night. Since the density of the atmosphere rapidly decreases with altitude, the filtering action of air in a vertical direction is limited and would be insufficient to protect an observer with fully dilated pupils. In this case, an atomic flash would be expected to cause permanent visual scotomata in all observers without protective glasses. This effect would be independent of the altitude of the burst, until the visual angle subtended by the fireball became less than about 10-12 minutes of arc. For a nominal weapon, with use of data from atmospheric detonations, this limiting altitude would be of the order of 75 miles. Since this is based on the most conservative figures, the actual limiting "safe" altitude would probably be from 5 to 10 times this figure.

Summary

With use of a high-intensity light source to produce chorioretinal lesions in the eyes of rabbits, cats, and guinea pigs, we determined, at different levels of retinal irradiance, the exposure time which produced an ophthalmoscopically visible lesion it was found that at irradiance levels greater than 2 cal. per square centimeter per second a radiant exposure of 1.0 cal. per square centimeter produced a threshold lesion. At irradiance levels less than 0.7 cal. per square centimeter per second lesions could not be produced at any exposure time through 10 seconds. Histological data on the nature of the lesions and course of healing are presented and discussed.

Mr. Joseph Basso assisted in construction of the apparatus and during the experimental procedure. Miss Marilyn Aldrich assisted during the experimental procedure.

Department of Radiation Biology, University of Rochester (20).

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Electromyography of Human Saccadic Eye Movements

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The purpose of this paper is to report the results of an electromyographic study of saccadic movements (rapid versions) performed during a previously reported study of coactivity of the human extraocular muscles.[1] The technique employed has been previously described.[2]

During a saccadic eye movement in any direction, there is increased electrical activity of all muscles except the one reciprocally inhibited by the required movements. The evidence for this is as follows:

In Figure 1, the arrows from above indicate the start of horizontal saccades, the first to the left, the second to the right. During each saccade, there is increased electrical activity in both vertical recti, suggesting cocontraction. The agonist during the first saccade (right medial rectus) manifests increased activity. After the saccade the activity of each of the muscles returns to the level required by the final position of the eye. The first muscle channel (right lateral rectus) should be disregarded for the time being. It is not working because of a poor insertion.

Cocontraction is defined as a simultaneous contraction of muscles which are normally antagonistic in their primary field of action. The apparent coactivity of the vertical recti and the increased activity of the agonist during the saccade, as in Figure 1, could not be immediately accepted because of the many artifacts inherent in electromyography of the extraocular muscles.[3] It is necessary to differentiate actual sustained motor unit activity from possible artifactual activity. We have seen how artifacts resulting from blinking (arrows, Fig. 2) can grossly suggest short bursts of motor unit activity. But blink responses are shorter in duration than the saccadic response and, in addition, characteristically give rise to slower potentials which appear as shifts in baseline (Fig. 2). Returning to Figure 1, we suspect that the potentials in Channel 1 during the saccade are artifactual, since we know we have a very poor insertion in the lateral rectus. We have evidence of its artifactual character rather than its being unit activity in that the medial rectus is inhibited during the

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From the Division of Ophthalmology, Department of Surgery, Stanford University School of Medicine, San Francisco (Drs. Tamler and Jampolsky). School of Optometry, University of California, Berkeley, Calif. (Dr. Marg). Hebrew University Hospital (Dr. Nawratzki).

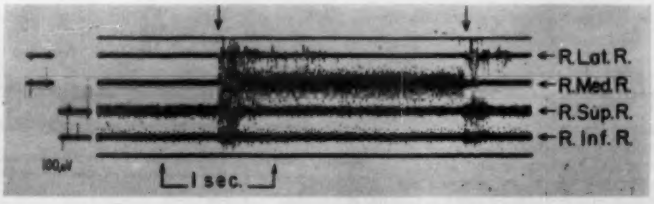


Fig. 1.—The arrows indicate start of a saccade, the first to the left, the second to the right. Channel 1 (right lateral rectus) is a poor insertion and not recording properly. Calibration is at left, and time scale is on bottom channel. Note increased activity of agonist (right medial rectus, first saccade) and auxiliary muscles (right superior and right inferior rectus) during the saccade and artifactual activity of first channel. Time scale shown here also applies to Figures 2, 3, and 4.

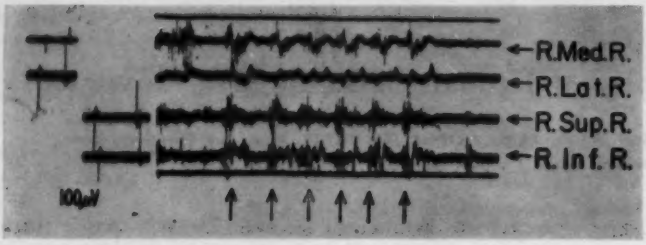


Fig. 2.—Arrows indicate eyelid blink. Note artifactual shifts in baseline and short bursts of "pseudoactivity" with each blink.

second saccade in Figure 1. Here, with a good insertion, no simulated activity occurs. If the apparent surge of activity in the agonist and auxiliary muscles were an artifact, then one would also expect the inhibited muscle (right medial rectus, second saccade, Fig. 1) to exhibit a similar increase in "activity." Further evidence is shown in Figure 3, in which there is no artifactual activity during saccades (arrows) in a procainized muscle (Channel 2 *) or in a muscle with a poor insertion (Channel 4). Furthermore, in Figure 4 the agonist (left lateral rectus) shows a sustained typical burst of motor activity during a saccade as compared to the irregular artifactual activity picked up by conjunctival electrodes inserted near but not into the vertical recti (Channels 3 and 4, Fig. 4).

Further elucidation of the nature of the apparent increased electrical activity in all muscles except the inhibited ones during a saccade is obtained by running the recording film at high speed during eye movements. Artifacts, such as occur with a blink, appear mainly as a succession of large shifts in baseline on high speed recording (Fig. 5). On the other hand, the trace of the agonist (Fig. 6) or auxiliary muscles (Fig. 7) during a saccade reveals a surge of typical motor unit activity.

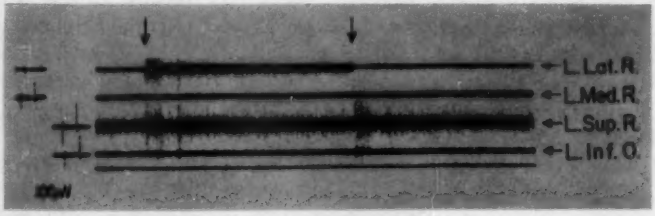


Fig. 3.—Arrows indicate start of saccades, first to left; second to right. Left medial rectus has a procaine-induced paralysis. Note increased activity of agonist (left lateral rectus, first saccade) and cocontraction of auxiliary (left superior rectus) during saccades but no activity, artifactual or otherwise, from electrode in procainized muscle. Channel 4 (left inferior rectus) is a poor recording because of poor insertion.

* The left eye actually moves to the right despite procaine-induced paralysis of the left medial rectus. A discussion of the possible reason for movement of this eye in face of paralysis of the agonist is outside the scope of this paper.

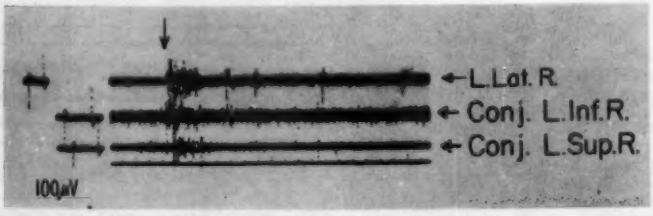


Fig. 4.—Arrow indicates start of saccade to the left. Channel 1 represents standard electrode inserted into left lateral rectus. Channels 2 and 3 represent standard electrodes inserted under conjunctiva near left inferior rectus and left superior rectus. Compare sustained activity in the agonist (left lateral rectus) with the artifactual irregular changes in Channels 2 and 3 during the saccade.

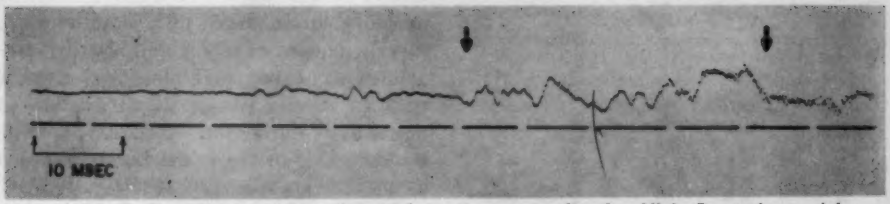


Fig. 5.—Fast film speed recording (1.5 meter per second) of a blink. It consists mainly of a series of large baseline shifts. Time scale here also applies to Figures 6, 7, and 8.

Björk [4] also noted increased activity of an auxiliary muscle, the inferior oblique, during rapid horizontal movements of the eye.

Therefore, we can conclude that during a saccade there is a burst of activity in the agonist, complete inhibition of the antagonist, and coactivity of the auxiliary muscles.† After the saccade is completed, all of these muscles appear to return to the level of activity that they would normally assume for that position of the eyeball.

The duration of saccades of varying degrees of excursion can be measured by combining electro-oculography (EOG) [5] with electromyography as in Figure 6. One need only measure the time elapsed between the start and the end of the slope of the EOG trace. This can be readily accomplished with the long and gently rising

† Because of the practical anatomical difficulty in obtaining a successful insertion into the superior oblique muscle under normal conditions, we make the likely assumption that this muscle behaves as do the other auxiliary muscles.

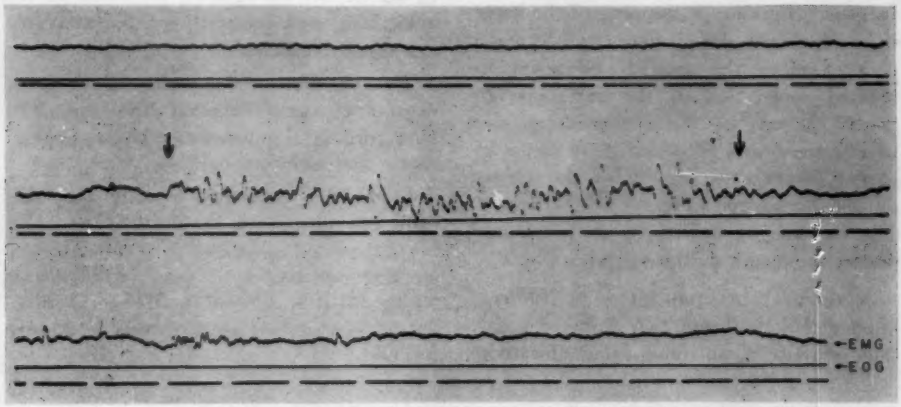


Fig. 6.—Fast film speed recording (2 meters per second) of agonist during a 26-degree saccade. Arrows indicate start and end of saccade. Lower trace is EOG. Note increased, essentially unchanging motor unit activity during saccade. The dash line is a horizontal reference line with which EOG slope can be compared.

Fig. 7.—Fast film speed recording (2 meters per second) of an auxiliary muscle (right medial rectus) during a vertical saccade. Arrow indicates start of saccade. Note increased activity (cocontraction) of right medial rectus during saccade.

TABLE

Angle of Saccade, Degrees	Mean Duration, Msec.	Mean Deviation *	N	Mean Angular Velocity, Degrees/Sec.
13	35.7	1.2	9	364.1
26	51.8	4.9	7	501.9
39	68.5	--	1	569.3
53	100.9	1.9	5	525.3

* Mean deviation equals the sum of the deviations, ignoring the sign, of each measurement from the mean, divided by the total number (*N*) of measurements.

EOG trace obtained with fast film-sweep speeds (2 m. per second in Fig. 6) and a D. C. amplifier. Average durations for various degrees of excursions obtained from repeated measurements in two subjects are listed in the Table.

Fast-film-speed electromyography directly confirms Westheimer's analysis which shows that saccadic eye movement is not ballistic.[6] Braking or stopping of the movement does not come about by decreased contraction of the agonist and active increased contraction of the antagonist towards the end of the movement as seen in Figures 6 and 8, where there is no apparent decrease in activity of the agonist during the saccade (Fig. 6) and no recordable increase in activity of the antagonist during the length of the saccade (Fig. 8).

A recent paper on this same subject[7] implies that there are two parts to a saccadic movement, an initial burst of activity in the agonist followed by a more uniform, orderly, pattern of motor unit activity. Examination of our high-film-speed saccade tracings reveals no apparent variation in unit activity during the saccade. Comparing the durations of the initial bursts recorded in the other paper (30 to 150 msec. for saccades of 2.5 to 40 degrees) with the saccade duration reported above in the Table, it is likely that what this recent paper describes as an initial burst is the entire saccade which is then followed by the level of sustained activity for that position no matter how the eye gets there. Neither do we find evidence of a second saccade following initial saccades of more than 15 degrees, as reported.

Summary

During a saccade or rapid version movement of the eye, there is a heightened burst of activity of the agonist, inhibition of the antagonist, and coactivity of the auxiliary extraocular muscles.

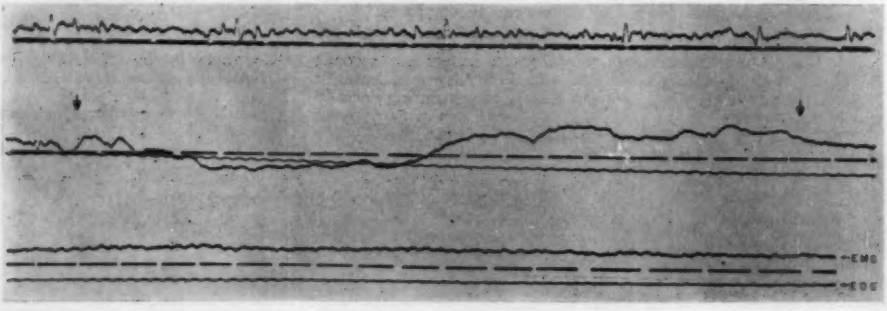
The duration of saccades of different degrees of excursions has been measured by recording simultaneously electro-oculography and electromyography.

Evidence is presented to show that saccadic eye movements are not ballistic.

Assistance was contributed by William Houweling, electronics engineer; Wilmer Renner, photographer, and Niles Roth, B.A., M.O.

Stanford University Hospital, Clay & Webster Sts. (15).

Fig. 8.—Fast film speed recording (2 meters per second) of the inhibited antagonist during a saccade. Arrows indicate start and end of saccade. Note no significant increase in activity during saccade. The dash line is a horizontal reference line for comparison with EOG slope.



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Tryptophan-Deficiency Cataract in Guinea Pigs

LUDWIG von SALLMANN, M.D.; MARY E. REID, Ph.D.; PATRICIA A. GRIMES, B.A., and ELEANOR M. COLLINS, Bethesda, Md.

Lens opacities have been described in rats on diets deficient in one of several essential amino acids. Such observations appear firmly established in tryptophan, phenylalanine, valine, and histidine deficiency; questionable when threonine or isoleucine were withheld from the diet, and negative in rats on diets lacking in methionine or arginine.[1-6] The frequency, course, and histology of the lenticular changes have not been sufficiently studied with the exception of the tryptophan-deficiency cataract. Here, the original observation of Totter and Day[1] and the detailed biomicroscopic description of the lesion by Buschke[7] were confirmed and extended by histological examinations of Ferraro and Roizin.[8] Later an attempt was made in this laboratory to analyze the effect of tryptophan deficiency on cell division and cell degeneration in the lens epithelium of rats,[9] but the small number of survivors in our series prevented the accumulation of sufficient data. Since guinea pigs can be maintained on a tryptophan-deficient diet for many months and develop early cataract, this laboratory animal is better suited for such an experiment. Moreover, the larger size of the guinea pig lens facilitates the analysis of the slit-lamp picture and the microscopic examination. The present investigation was undertaken for these reasons and also in view of the possibility of studying quantitatively the tryptophan requirement for securing clearness of the lens over long periods.*

Materials and Methods

Male guinea pigs of the Hartley strain were placed on the experimental diet when they were 3 to 5 days old. The basal diet contained 0.1% L-tryptophan and was composed of the following ingredients in percentage amounts: purified soybean protein (Drackett), 10; gelatin, 10; corn oil, 7.3; sucrose, 10.2; cellophane spangles, 15; cornstarch, 20; cerelose, 13.9; potassium acetate, 2.5; magnesium oxide, 0.5; salts, 6; choline chloride, 0.2; ascorbic acid, 0.2; inositol, 0.2; a mixture of eight essential amino acids (no arginine or tryptophan) plus glutamic acid, cystine, and tyrosine, 4.0, and liberal amounts of vitamins.† The guinea pigs were divided into several groups, one of which was fed the basal tryptophan-deficient diet, while the remaining groups were fed the basal diet plus varying supplements of tryptophan. These supplements ranged from 0.02% to 0.1%.

Weight and appearance of the animals were recorded weekly. Biomicroscopic examinations were also carried out at weekly intervals with the Goldmann slit lamp under × 20 magnification. Both eyes from 136 guinea pigs used in this experiment were enucleated, imbedded in celloidin, and stained with hematoxylin and eosin.

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From the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness (Dr. von Sallmann, Miss Grimes, Mrs. Collins), and the Laboratory of Nutrition and Endocrinology, National Institute of Arthritis and Metabolic Diseases (Dr. Reid), National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

* A review of the morphology, physiology, and pathology of the lens epithelium presented at the XVIII International Congress of Ophthalmology, Brussels, Sept. 8-12, 1958, contains a preliminary report of the histologic changes in tryptophan-deficient guinea pigs.

† This diet is discussed by Dr. Reid in another article.

Early histological changes were studied in groups of animals killed one and two weeks after the experimental diet was started. The major portion of the series of animals was killed at intervals of from 4½ to 14 weeks. A cytologic study of the lens epithelium in whole mounts had to be omitted, because the separation of the epithelium from the surface of the lens cortex after the Feulgen reaction cannot be achieved in young guinea pigs.

To amplify previously reported observations on the rat lens epithelium several litters of rats (52 animals) were placed on tryptophan-deficient diets of various types and were observed biomicroscopically. Nine weeks after feeding began the eyes were enucleated. All right eyes were prepared for cytologic examination of the lens epithelium in whole mounts after being subjected to the Feulgen technique. The left eyes were used for histologic studies, and the results were compared with those obtained in guinea pigs.

Results

Clinical Observations.—All animals gained weight while on the basal diet containing 0.1% L-tryptophan, although their growth rate was moderately decreased to three-fourths that of normal. Most guinea pigs initially lost hair to different degrees. This partial or almost complete alopecia was transient. New fur developed despite continued feeding of the tryptophan-deficient diet.

Biomicroscopic Observations.—The first changes were observed in one-third of the animals (7 out of 21) one week after they were placed on the experimental diet. At the two-week interval about four-fifths of the guinea pigs (20 out of 24) showed incipient lesions. All of the animals on this diet developed cataract when the experiments were continued longer. The earliest signs of fiber damage consisted of fine subcapsular diffuse or striate silky opacities in the posterior cortex and, less frequently, of delicate lines or nets near the surface of the anterior cortex. This change produced occasionally a diffuse moiré effect. In a few instances the lesions centered around the suture system. Vacuole formation and the development of distinct gray flaky changes were rare occurrences.

Fig. 1.—Guinea pig eye with advanced stage of tryptophan-deficiency cataract. The cataractous process does not involve the superficial layers of the cortex. A clear part of the lens is seen between the margin of the iris and the perinuclear opacity in the upper part of the photograph.

After four weeks the cataractous changes assumed a more characteristic pattern. They then involved predominantly the perinuclear zone and were often clearly connected with the suture system. Grayness of the anterior suture lines and signs of a marked difference of refractive index between the nuclear and cortical portion were noted at this stage. Total reflection of the light beam at the equator of the nucleus created a picture similar to that seen at the lens equator in subluxation of the human lens (Fig 1).

In the following weeks a perinuclear shell-like opacity became progressively more pronounced and subsequently extended to the surface of the lens cortex leading to the development of total cataract. The involvement of various parts of the lens and the onset of the first changes differed somewhat among animals of the same group, but the over-all nature of the advancing opacification was not altered by such variations.

Histologic Observations.—Histologic examination was performed on 12μ thick sections of celloidin-imbedded eyes. Except for corneal vascularization in a great number of preparations, there were no abnormal

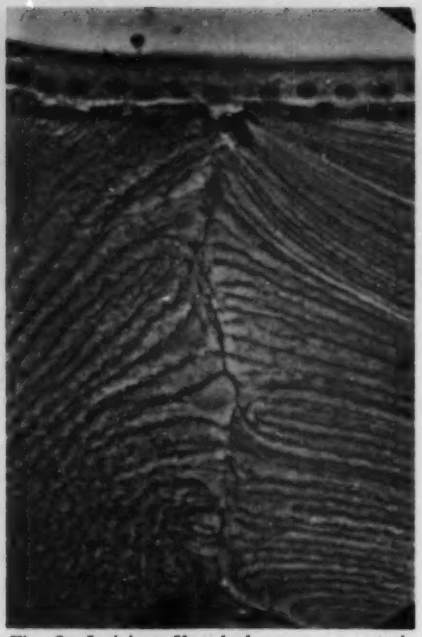


Fig. 2.—Incipient fiber hydrops at an anterior suture, two weeks after the experimental diet was started. Guinea pig; hematoxylin and eosin, phase contrast; × 504.

findings in parts of the eye other than the lens. The changes seen in animals which had been on the deficient diet for one and two weeks can be grouped into two categories. First, the ends of the lens fibers at the site of the sutures frequently exhibited hydropic swelling in the anterior and posterior cortex (Fig. 2). The second change consisted of well-delineated round or oblong formations of granular structure which lined the posterior capsule (Fig. 3). Most likely this lesion represents cross sectioned hydropic fibers and may be the correlate of the silky opacification seen with the biomicroscope. The lens epithelium including the germinative zone and the bow nuclei appeared normal, although some irregularities in the distribution of deep-seated bow nuclei and an increase of the involutionary changes of these nuclei in deeper cortical layers might have significance. In two instances the histopathology differed from the typical picture. Circumscribed epithelial proliferations were observed in one eye at the subcapsular end of an anterior suture (Figs. 4 and 5). Some fibers joining there were hydropic. In another animal, large cystic spaces and smaller vacuoles were located in the deeper layers of the posterior cortex.

At the four-week interval and later, swelling of fibers in the perinuclear area was the predominant change. The loss of the fine striation and the increase of the fiber volume were most frequently observed near the sutures, although occasionally they did occur at other sites underneath the capsule. At a later phase, the involved parts of neighboring fibers confluated and disintegrated to homogenous granular clumps,

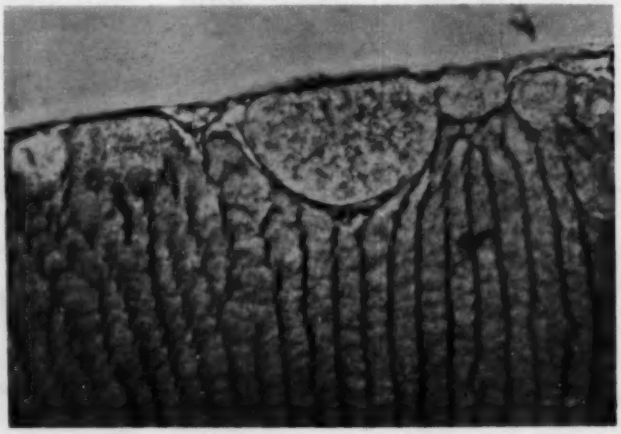


Fig. 3.—Incipient subcapsular changes in the posterior cortex, two weeks after the deficient diet was started. Later this cortical layer resumes a normal appearance. Guinea pig; hematoxylin and eosin, phase contrast; × 504.

Fig. 4.—Hydropic fiber swelling in deep layers of the anterior cortex, extending forward along a suture, two weeks after the deficient diet was started. The epithelium around the end of the suture shows beginning multiplication. Guinea pig; hematoxylin and eosin, phase contrast; × 504.

particularly in deeper layers of the anterior cortex in an area around the lens axis (Fig. 6). The damage progressed along the suture forward to the anterior surface and especially to the anterior pole (Fig. 7). This lesion assumed later on cross section a triangular shape consisting of granular debris. In the posterior cortex similar decomposition of lens fibers was located in supranuclear and middle layers, whereas subcapsular portions had reassumed the normal anatomical characteristics. The sharp line of demarcation between the cortical and nuclear portion which was described in the biomicroscopic picture was well demonstrated histologically and accentuated when phase contrast microscopy was used on these sections (Fig. 8).

When cataractous changes advanced further the involvement of the cortex and nucleus proceeded in the usual pattern. The feature which did distinguish this cataractous process from other histologically examined forms of experimental lenticular opacities (cataracts due to ionizing radiation or treatment with myleran, galactose, alloxan, and mimosine) was the preservation of the equatorial tissue elements, including the germinative epithelium, the bow cells, and the fibers. Thus even when destruction of the cortex was extensive the architecture of the equatorial area and the histological characteristics of composing structures remained undisturbed as shown in Figure 9.

The epithelium could not be examined in flat mounts. The changes which can be discerned only with this technique may have escaped the study of the histologic sections. For this reason additional series of experiments were conducted on rats and will be reported subsequently. The epithelium of the guinea pig lens underwent multiplication at circumscribed sites near the location of sutures, particularly around the anterior

Fig. 5.—Knob-like proliferation of the lens epithelium at the ending of an anterior suture, two weeks after the deficient diet was started. The fiber hydrops here is not seen as well as in adjacent sections. Guinea pig; hematoxylin and eosin, phase contrast; × 504.

Fig. 6.—Decomposition of fibers to clumped homogeneous masses in the deep axial part of the anterior cortex, six weeks after deficient diet was started. This change later progresses and forms, on cross section, a wedge-shaped granular mass. Guinea pig; hematoxylin and eosin, phase contrast; × 504.

Fig. 7.—Coalescence and aggregation of disintegrated fiber cytoplasm near the anterior pole of the lens nucleus, extending forward along a suture line. Guinea pig; hematoxylin and eosin, phase contrast; × 504.

Fig. 8.—The hydropic fibers of the superficial and deep part of the lens cortex are divided by a sharp line. Guinea pig; hematoxylin and eosin, phase contrast; × 504.

Fig. 9.—Normal lens equator overlying advanced perinuclear and nuclear cataractous changes, eight weeks after deficient diet was started. Guinea pig; hematoxylin and eosin, phase contrast; × 112.

pole of the lens. This was mentioned as a rare finding at the two-week interval but occurred more frequently at later stages. The sometimes extensive proliferation and formation of multilayered patches or knobs seemed to take place when the decomposed cortical matter around the sutures reached or approached the epithelium. Figure 4 illustrates such epithelial proliferation, which was considered as a response to a stimulus connected with disintegration of cortical fibers. The epithelial changes might be the histologic counterpart of the gray plaques visible in vivo with the slit lamp at the superficial terminations of sutures. The fine lines and delicate nets observed with the biomicroscope during the earliest stage of damage were not identified in the sections.

Tryptophan Requirements for Preserving Transparency of Lens.—Small supplements of tryptophan when added to the basic diet which contained 0.1% of the amino acid clearly influenced onset and extent of the cataractous changes in most animals. As little as 0.02% tryptophan caused the growth curve of the animals to approach that of normal. For semiquantitation of the effects on the lens the severity of the lesions was graded arbitrarily on the basis of the biomicroscopic and of the histologic appearance as suggestive (+), incipient (++), extensive (+++), and far advanced (++++). The Table shows the dependency of the cataractous processes on the quantities of the supplement. Since, as a rule, histologic changes were analogous to biomicroscopically observed signs of damage, both are tabulated together. Of the various tryptophan supplements fed, that is, 0.02%, 0.03%, 0.05%, 0.06%, and 0.1%, only the experiments in which 0.02%, 0.03%, and 0.1% were added to the basic diet were used in the Table, because these groups comprised a sufficient number of animals.

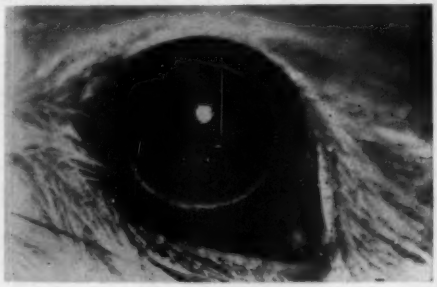
Those animals receiving the basal diet showed incipient to advanced lens changes even at one or two weeks and uniformly at four and one-half weeks, while at six and eight weeks cataracts were extensive or far advanced. It is apparent from the Table that the supplement of 0.02% afforded some protection, since the lens changes observed in these animals at all time intervals were considerably less widespread than those of the guinea pigs on the basal diet. As late as eight weeks only two of five guinea pigs in this group had extensive cataractous changes, while the lenses of the remaining three were classified as suggestive, incipient, and normal. An increase of the supplement

Cataractous Changes Varying with Tryptophan Content of Diet *

Time After Start of Diet, Wk.	Basal Diet	Tryptophan Supplement +0.02%	+0.03%	+0.05–+0.1%
	+++	++		0
4½	++	+		0
	++	+		0
	++++	+		0
		+		0
	++++	+	++	0
	+++	+	++	0
	++++	+++	0	0
6	+++		++	0
	++++		+	0
	++++			0
	++++			0
	++++			0
	+++			0
	++++	+	0	0
	++++	++	+	0
	++++	0	+	0
8	++++	+++	0	0
	+++	+++	0	
	++++		0	
	++++		+	
	++++		+	
			0	

* Suggestive, +; incipient, ++; extensive, +++; far advanced, ++++.

Fig. 10.—Rat eye, four weeks after deficient diet was started. The strongly reflecting contour separates the lens nucleus and the clear cortex. The cornea shows vascularization.



to 0.03% appeared to be proportionately more effective in protecting against opacities, since at eight weeks five of nine animals had clear lenses, while the remaining four had only suggestive changes. With 0.1% tryptophan added to the diet, no opacities developed. In general, the results of histological examination were in good agreement with those obtained by biomicroscopy and thus supported the reliability of the in vivo study.

Observations on Rats Fed a New Tryptophan-Deficient Diet.—In a previous study [9] conducted on rats in this laboratory the high death rate of the animals fed the tryptophan-deficient diet of Totter and Day [1] precluded prolonged experiments. During the first two weeks the effect of feeding this diet consisted of a moderate depression of cell division in the lens epithelium, which was followed by a similar slight increase of the mitotic activity also lasting two weeks. After six weeks cataractous changes developed, and at this time the number of dividing cells apparently tended to decline. However, only a few animals survived till the later stages. Throughout the duration of the experiment signs of cell degeneration in the lens epithelium were absent.

To further these investigations several new diets have been used to produce tryptophan deficiency in rats. Although the results and discussion of the experiments will be reported later when more data have been collected, observations of one series of animals are described here to compare the histologic and cytologic changes in rats and guinea pigs. The basal diet was of the following percentage composition: purified soybean protein (Drackett), 5; gelatin, 5; corn meal, 40; corn oil, 10; sucrose, 27.4; salts, 6; choline chloride, 0.1; inositol, 0.1; amino acid mixture, 1.4, and liberal amounts of vitamins. The total tryptophan content of this diet was approximately 0.08%. Sprague-Dawley rats were started on the experimental diet at 25 days of age. A control group received the basal diet, to which

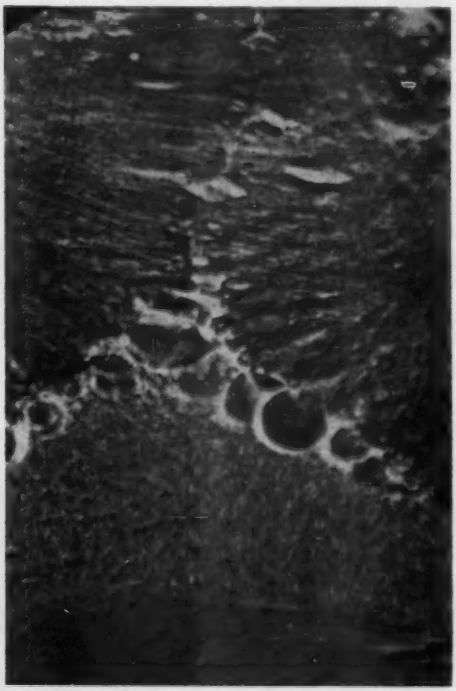


Fig. 11.—Wedge-shaped granular matter around anterior pole of lens nucleus, nine weeks after the deficient diet was started. Rat; hematoxylin and eosin, phase contrast; × 504.

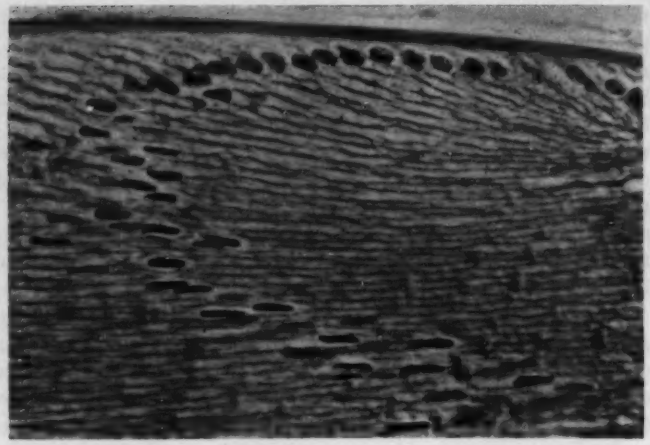


Fig. 12.—Same lens as in Figure 11, equatorial area of normal morphology. Hematoxylin and eosin, phase contrast; reduced about 10% from mag. × 504.

0.2% tryptophan was added. The animals were observed for nine weeks.

Biomicroscopically gapping of suture lines and a fine diffuse opacity in the posterior cortex were noted after four weeks in the animals on the deficient diet. Two weeks later a difference of the refractive index between cortex and nucleus was the most striking feature (Fig. 10). Lens opacification subsequently developed and progressed predominantly in the perinuclear area and assumed a pattern which resembled that observed in guinea pigs.

Histologically the changes in the rat lens were also similar to those in the guinea pig lens. The involvement of deep layers with decomposition of the fiber cytoplasm around the anterior pole resulted again in the formation of a wedge-like lesion of amorphous granular texture spreading forward along the suture line (Fig. 11). Here, as in the guinea pigs, the cellular elements in the equatorial area retained their integrity despite the severe changes in the cortex and lens nucleus (Fig. 12).

When the whole Feulgen-treated lens was bisected and examined under low magnification, the zone of bow nuclei appeared broadened and showed irregularities which suggested partial migration of the nuclei backward.

The examination of the lens epithelium in flat mounts after nine weeks confirmed previous results. The mitotic counts were decreased by about 25% when compared with the counts on control animals (95:125 mitoses per preparation). Even in this late stage no signs of nuclear fragmentation or other forms of nuclear degeneration were apparent under the light microscope.

Comment

Guinea pigs have not been used in the past for investigating lens changes in tryptophan deficiency. Data on the histopathology of the lens of deficient rats have been provided by Ferraro and Roizin.[5] Five to eleven weeks after the animals had been placed on the experimental diet these investigators observed hydropic changes in the lens fibers of the cortex and sometimes vacuole formation; later, degenerative changes of the fibers progressed and led to disintegration of cortical, perinuclear, or nuclear structures. Occasionally the damaged parts assumed a lamellar, surface-parallel orientation or were patchy in appearance. The most remarkable observation in tryptophan-deficient cataract, the preserved equatorial tissue components, was not mentioned.

In the present study the sequence of biomicroscopic and histologic lens changes in guinea pigs resembled those seen in rats. However, in contrast to the actual loss of weight found in rats on the diet

of Totter and Day, the guinea pigs on a diet containing 0.1% tryptophan grew relatively well. Nevertheless, the tryptophan-deficient guinea pigs developed cataractous changes earlier than the rats and lenticular damage progressed despite continued growth.

With the tryptophan supplement of 0.02% there was practically normal growth, although incipient lens opacities developed in all animals and were extensive in some. With the addition of 0.03% tryptophan to the diet containing 0.1% of the amino acid a level was reached at which the lens damage was reduced to occasional fiber hydrops at various sites of the cortex; pronounced disintegration of the cytoplasm and advanced cataract appeared toward the end of the 14 weeks of observation. Thus the protection of the clear lens by the supplements gradually increased with the dose and was absolute for the observation period when 0.1% tryptophan was added to the basal diet.

In both species incipient hydropic swelling involved the subcapsular ends of the fibers at their junction along the suture systems. The bow nuclei belonging to these fibers did not visibly deviate from the normal either in morphology or in their position within the sweep of the lens bow. Occasionally in the rat the bow nuclei appeared to fan out into deeper parts of the lens and exhibited varying signs of degeneration. The germinative epithelium was of normal appearance. The gray suture lines seen at an early stage in the superficial cortex of guinea pigs may be the biomicroscopic counterpart of the hydropic change of the fiber ends, and the gapping of sutures in the rat anterior cortex might express the fact that the growth has stopped at the fiber terminations. Extensive cytoplasmic damage seemed to take place first in the deeper layers of the cortex, giving rise to perinuclear lesions which are unknown in other types of histologically studied experimental cataracts. It has been described that lens opacities produced by ionizing radiation or radiomimetic drugs involve first the equatorial epithelium, the bow nuclei, and the equatorial young fibers. In galactose and alloxan cataract the young lens fibers in front of the lens bow succumb first to the toxic effect.[9] In mimosine cataract the germinative epithelium seems to be singled out for early destruction.[10]

Recovery experiments have not been carried out on guinea pigs, but the observations of Ferraro and Roizin[5] indicate that the cataractous changes regress and the damage due to the amino acid deficiency did not advance when adequate tryptophan was provided. A similar course of recovery was observed in galactose cataract.[9]

Summary

Young guinea pigs fed a tryptophan-deficient diet containing 0.1% of the amino acid develop incipient cataractous changes one or two weeks after the feeding is started.

The first histologic lesions consist of hydropic swelling at the ends of the fibers, particularly at the sutures. Later the histopathology involves the deep cortex and spreads from here along the suture towards the surface.

Lens epithelial cells do not undergo degeneration, although they may multiply around the sutures. All components of the lens equator preserve their morphologic integrity in the presence of advanced cataract in contrast to any other experimental cataract studied so far.

Small supplements of tryptophan added to the basal deficient diet delay onset and prevent extensive lenticular damage. When the supplements are increased to about 0.1% cataractous changes do not develop.

Whereas rats suffer loss of weight on tryptophan-deficient diets which cause cataract, guinea pigs on the diet used in this study grow at a rate which is only moderately decreased, yet they rapidly develop lenticular changes.

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Effect of Demecarium Bromide (BC 48) on Intraocular Pressure in Man

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It is now widely held that the treatment of chronic simple glaucoma should be conservative, because it is realized that the surgical results are very indifferent in this form of glaucoma as opposed to the angle-closure variety. Present-day research is directed toward finding the etiology of this condition and into the evolution of new remedies which may help the conservative control of glaucoma once it is established. While there is no universal agreement that the changes at the optic nerve head and the changes in intraocular pressure run in parallel, it is nevertheless agreed that a rise in the intraocular pressure is to be avoided, and, even though this does not always completely arrest the glaucomatous process, there is evidence to support the notion that control of the intraocular pressure constitutes the only known means by which the pathological process can be influenced.

A number of new powerful cholinesterase inhibitors have been synthesized and have been reported from time to time to be very beneficial in the treatment of glaucoma. Diisopropyl fluorophosphate (DFP) was the first of these very powerful drugs and was reported on by Leopold.[1] It has, however, a number of disadvantages, mainly the lack of stability except in an oily solution and the fairly intense discomfort which the patients experience. Gittler and Pillat[2] have recently reported on the use of a new cholinesterase-inhibitor, demecarium bromide. Decamethylene bis-(m-dimethylaminophenyl N-methyl-carbamate) dimethobromide is water-soluble and stable for indefinite periods[3]; applied as an ophthalmic solution, it inactivates cholinesterase. The resultant accumulation of acetylcholine produces miosis, some spasm of accommodation, vasodilation of conjunctival vessels, and an increased permeability of the blood-aqueous barrier. There is an accompanying drop in intraocular pressure. The local effects of the drug in the eye can be antagonized by the use of atropine with or without pyridine-2-aldoxime methiodide (2-PAM).[4]

The present study was designed to assess the ocular hypotensive effect of demecarium bromide in normal and glaucomatous eyes and also to evaluate the mechanism by which this hypotension is produced.

Normal Eyes

(a) Method.—The group with normal eyes investigated consisted of patients admitted for the treatment of squints and plastic conditions of lids, as well as some patients undergoing treatment in other departments. Glaucoma was excluded by tonography, diurnal tension curves, examination of the fundus, and visual field studies. Tonography was carried out with a Mueller electronic tonometer and a Honeywell-Brown recorder and was corrected when necessary for scleral rigidity, which was estimated with the applanation tonometer and the 10 gm. Schiøtz weight with use of the 1955 Friedenwald calibra-

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Demecarium Bromide (BC 48, Humorsol) was supplied by Merck Sharp & Dohme Co., Ltd., Montreal.

TABLE 1.—*The Effect of 0.25% Demecarium Bromide on Intraocular Pressure in Normal Eyes*

	Intraocular Pressure, Mm. Hg				Facility of Outflow, Cu. Mm/Min/Mm. Hg			
	Treated Eye		Untreated Eye		Treated Eye		Untreated Eye	
	Before	After	Before	After	Before	After	Before	After
1	14	7	10	11	0.26	0.37	0.22	0.23
2	16.5	8	18	19	0.16	0.24	0.16	0.17
3	13	9	17	19	0.21	0.44	0.25	0.22
4	15	6	17	13	0.25	0.44+	0.33	0.28
5	15	4	15.5	14	0.17	0.34	0.26	0.22
Av.	14.6	6.8	15.5	15.4	0.21	0.37	0.24	0.22
% Change		−53		−0.64		+76		−8

tion. A drop of 0.25% or 0.1% demecarium bromide was instilled in one eye only, and three hourly tension checks were carried out during the day with a final reading at 10 p. m. and the first morning reading at 6 a. m. Tonographies were carried out at 24-hourly intervals, and the study was continued until the effect of the drug had worn off. The patient's other eye acted as a control.

(b) Results.—Five nonglaucomatous patients had one drop of 0.25% demecarium bromide instilled into one eye. All eyes treated with 0.25% demecarium bromide showed a very pronounced fall in the intraocular pressure. The untreated eyes, which served as a control, showed no more than the daily diurnal variation in pressure. The intraocular pressure started to fall after 10 to 21 hours after the instillation of the drops. There was frequently a slight rise of pressure amounting to no more than 3 to 4 mm. of Hg prior to the hypotensive phase. The average percentage fall of pressure was 53%, whereas the nontreated eye averaged a fall of less than 1%. All the treated eyes revealed a considerable increase in facility of outflow (*C*), the average increase being 76%. The untreated eyes revealed a very slight decrease of facility of outflow during the same period of time. The results in these five persons are tabulated in Table 1 and Figures 1 and 2.

Three patients had 0.1% demecarium bromide instilled into one eye; all three showed a profound fall in the intraocular

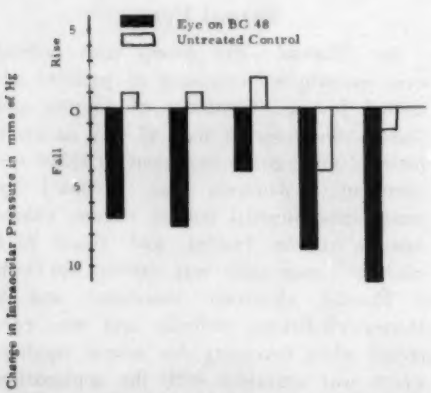


Fig. 1.—Effects of 0.25% demecarium bromide on the intraocular pressure in five nonglaucomatous eyes.

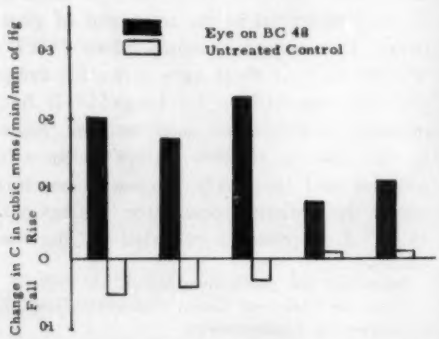


Fig. 2.—Effects of 0.25% demecarium bromide on the facility of outflow (*C*) in five nonglaucomatous eyes.

TABLE 2.—*The Effect of 0.1% Demecarium Bromide on Intraocular Pressure in Normal Eyes*

	Intraocular Pressure, Mm. Hg				Facility of Outflow, Cu. Mm/Min/Mm. Hg			
	Treated Eye		Untreated Eye		Treated Eye		Untreated Eye	
	Before	After	Before	After	Before	After	Before	After
1	16	7	16	15	0.19	0.43	0.18	0.19
2	10.5	3	15	12	0.19	0.30	0.15	0.18
3	13	3	13	12	0.21	0.45	0.24	0.26
Av.	13.1	4.3	14.6	13	0.19	0.39	0.18	0.21
% Change		−65		−10		+105		+14

pressure of the treated eye, whereas the untreated eye showed only the diurnal variation in intraocular pressure. Intraocular pressure started to fall in five to six hours. The average fall in the treated eye was 65%; the average fall in the untreated eye was 10%. Tonographic studies revealed an increase in the facility of outflow in the treated eye which was very much higher than the slight increase in facility of outflow in the untreated eye. The average increase in the facility of outflow of the treated eye was 105%; the average rise in the facility of outflow in the untreated eye was 14%. The results in the three patients are shown in Table 2 and Figures 3 and 4. The return to normal of intraocular pressures and facility of outflow took place in from 60 to 96 hours.

(c) Side-Effects.—Miosis commenced within one-half to one hour in the treated eye. The pupils became pinpoint and remained miotic for a longer period of time than the ocular hypotension. With the exception of one patient, all treated eyes showed a fair amount of vasodilation. The patients had some blurring of vision owing to a change of their refraction toward myopia. Most patients had some discomfort in the treated eye; some complained of headache in the overlying brow. One patient showed a flare and cells in the anterior chamber. No systemic side-effects were encountered in this group. In one patient the drop of demecarium bromide produced a considerable fall in the intraocular pressure during the day, but this was accompanied by a very considerable

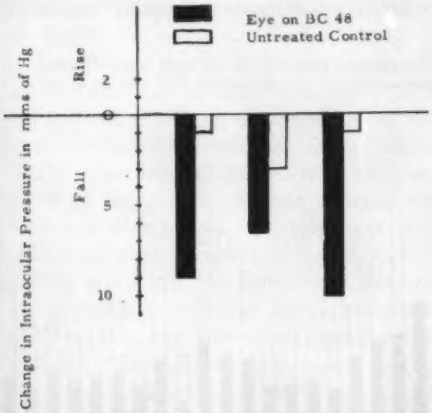


Fig. 3.—Effects of 0.1% demecarium bromide on the intraocular pressure in three nonglaucomatous eyes.

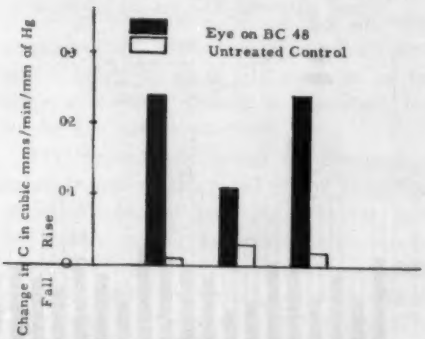


Fig. 4.—Effects of 0.1% demecarium bromide on the facility of outflow (*C*) in three nonglaucomatous eyes.

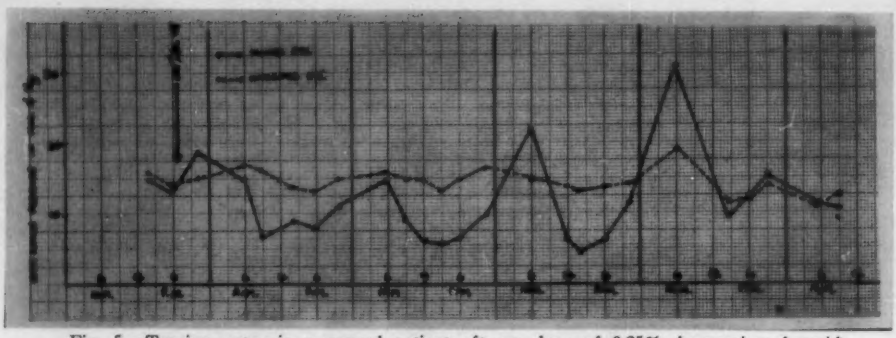


Fig. 5.—Tension curve in a normal patient after a drop of 0.25% demecarium bromide. The treated eye showed a fall of intraocular pressure but exaggerated diurnal variations of pressure.

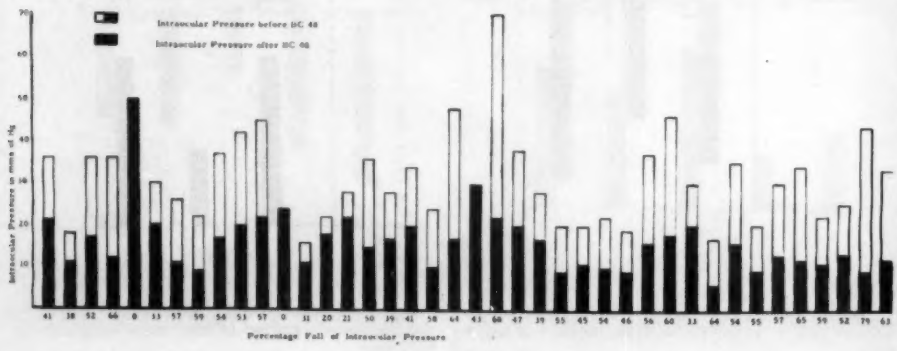
exaggeration of the diurnal tension variation, the affected eye showing pressures up to 31 mm. of Hg at 6 a. m. (Fig. 5). The peaks of tension completely vanished when the effect of the drug had worn off.

Glaucomatous Eyes

(a) Study.—Forty eyes with chronic simple glaucoma not operated on were treated with 0.5%, 0.25%, and 0.1% of demecarium bromide. Most patients were started on the drug because of failure to control intraocular pressure with other miotics with or without the addition of carbonic-anhydrase-inhibitors. A few patients were started on demecarium bromide as the initial treatment. Two of the eyes showed absolute glaucoma. Eyes with angle-closure glaucoma were not included in this study because experiences with similar drugs suggest some danger of using these drugs in this form of the disease. All patients were in hospital for diurnal pressure studies and stabilization. The fall of intraocular pressure recorded was the maximal reduction of intraocular pressure attained at equivalent times of day. Tonographic studies were carried out at 24-hourly intervals. The present study reports only on the hypotensive effect of demecarium bromide in glaucoma; a subsequent paper will deal with the problem of long-term control of this condition with the drug.

(b) Results.—Thirty-eight of the forty eyes treated with demecarium bromide showed a satisfactory drop in intraocular

Fig. 6.—Effects of demecarium bromide on intraocular pressure in 40 eyes with chronic simple glaucoma. The changes in intraocular pressure shown in millimeters Hg and as a per cent fall.


Intraocular Pressure before DC 48
Intraocular Pressure after DC 48
Intraocular Pressure in mm of Hg
Percentage Fall of Intraocular Pressure

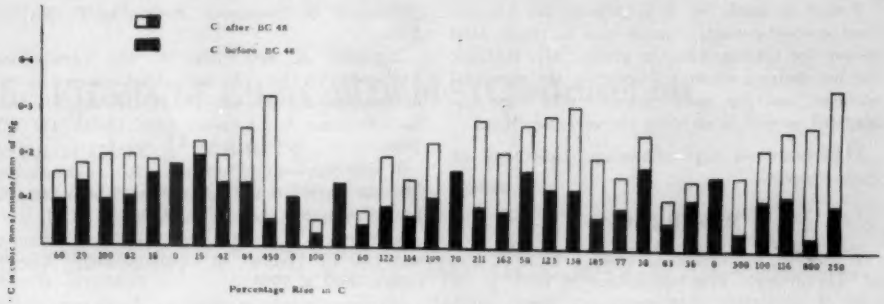


Fig. 7.—Effect of demecarium bromide on facility of outflow (C) in 34 eyes with chronic simple glaucoma. The changes in (C) shown in cubic millimeters per minute per millimeter Hg and as a per cent change.

pressure. The two eyes which failed to respond to the drug were both absolute glaucomatous eyes. Figure 6 illustrates the fall of intraocular pressure in the individual eyes tested. The average percentage fall of intraocular pressure in the 40 eyes was 48%. The first fall of intraocular pressure noted in the 40 eyes occurred after an average latency of 13 hours. The average time for the maximal fall of intraocular pressure to take place was 34 hours. Satisfactory tonographic studies were carried out on 34 of the 40 glaucomatous eyes. The average increase in the facility of outflow was 121%. In four eyes there was no increase in facility of outflow in spite of the fact that there was a significant fall in the intraocular pressure. The tonographic changes are graphically presented in Figure 7.

(c) Side-Effects.—Side-effects in the glaucomatous group of patients were identical with those already described for normal eyes. Demecarium bromide, 0.5%, caused fairly considerable local symptoms, and some of the patients showed systemic disturbance with nausea, vomiting, and some abdominal pain. In lower strengths, namely, 0.25% and 0.1%, the side-effects were entirely ocular and except on very rare occasions did not necessitate cessation of therapy. The long-term tolerance of patients to demecarium bromide will be discussed in the paper dealing with long-term control of glaucoma with the drug.

Summary

The effects of a new synthetic powerful cholinesterase-inhibitor, demecarium bromide, on the intraocular pressure in man are described.

In the normal human eye demecarium bromide produced a very marked fall in intraocular pressure which came on after 12 hours of instillation and persisted for three to five days. Tonographic studies revealed a marked increase in the facility of outflow (C).

Thirty-eight out of forty eyes with chronic simple glaucoma showed a significant and considerable drop in the intraocular pressure after instillation of 0.25% or 0.1% demecarium bromide. The two eyes which failed to respond were absolute glaucomatous eyes.

Thirty of thirty-four eyes with chronic simple glaucoma showed a considerable increase in the facility of outflow on tonographic study. Three out of the four eyes which failed to show any increase in facility of outflow showed a significant fall in the intraocular pressure.

The hypotensive action of demecarium bromide was accompanied in the great majority of normal and glaucomatous eyes by intense miosis, some spasm of accommodation, vasodilatation of the conjunctival vessels, ocular discomfort, and headache in the brow overlying the treated eye. The unpleasant side-effects tended to wear off with continuous use of the drops.

I want to thank Dr. R. G. Murray for his constant encouragement. I wish also to thank Miss Bower for helping with the graphs, Mr. B. Cook for his untiring efforts of securing the nocturnal tensions, and the many patients who have cooperated so well in securing the necessary data.

Department of Ophthalmology, University of Saskatchewan.

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The Effects of Ethoxzolamide (Cardrase) on Intraocular Pressure

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The carbonic anhydrase inhibitors, particularly acetazolamide (Diamox), have become a standard adjunct in the short-term management of the glaucomas since they were first evaluated by Becker,[1] in 1954. There are now numerous reports in the literature which indicate that long-term therapy is effective with these compounds without any obvious ill effect on the ocular tissues. The greatest number of failures in long-term control of the glaucomas with carbonic anhydrase inhibitors to date have been due to the large proportion of side-effects which have frequently necessitated cessation of therapy; only relatively few cases have become truly refractory. A number of newer carbonic anhydrase inhibitors are being evaluated in a search for a more powerful inhibitor with minimal side-effects in the dosage required.

Ethoxzolamide (Cardrase) is a new potent carbonic anhydrase inhibitor the use of which in ophthalmology has been reported on, particularly in the therapy of intraocular inflammation, by Gordon,[2] and in the treatment of glaucoma, by Posner.[3] This communication deals with the short-term effects of ethoxzolamide on intraocular pressure in normal subjects and patients with the various forms of glaucoma. The drug has been used in this clinic for just over one year, and this period was not considered long enough for a follow-up study of the use of this drug in the management of chronic simple glaucoma. Such a report is to follow.

Submitted for publication Feb. 4, 1959.

From the Glaucoma Clinic, University Hospital, University of Saskatchewan.

Cardrase supplied by The Upjohn Company, Kalamazoo, Mich., who also supported the investigation with a grant.

Ethoxzolamide is 6-ethoxy-2-benzothiazole sulfonamide.[4] It is a pure white crystalline solid, odorless and tasteless. It is practically insoluble in water and forms soluble salts with alkali. It is stable and nonhygroscopic. In vitro experiments show a 50% inhibition of carbonic anhydrase activity in a concentration of 2.7×10^{-8} moles.[4] In vivo studies on animals showed excellent diuretic responses in doses of 2.5 to 20 mg. per kilogram with an increase in urinary volume and urinary sodium and potassium excretion. These effects were highest for the first six hours after administration. Toxicity studies yielded an acute LD_{50} of greater than 1,000 mg. per kilogram. No drug-related organ lesions were found on subacute and chronic feeding experiments on animals at dose levels of 10 to 100 mg. per kilogram.[4]

In human subjects administration of ethoxzolamide has failed to show any organ sensitivity or drug-related lesion. There are side-effects, particularly with higher dosage, but these can be reduced in most cases by reducing the dose. The side-effects are similar to those reported with acetazolamide, but patients who do not tolerate acetazolamide often tolerate ethoxzolamide and vice versa.

Normal Eyes

A. Investigation.—The action of a single dose of ethoxzolamide was studied in 52 normal eyes. This group included medical students and patients seen because of other ocular disorders. Glaucoma was excluded by diurnal tension curves, tonographic studies, normal field studies, and normal appearance of the optic nerve head. The tension curves were such as to exclude pa-

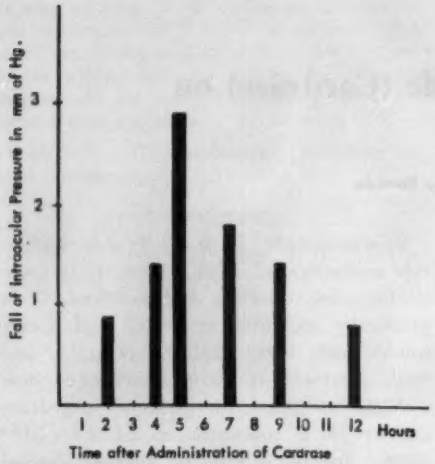

Fig. 1.—Average fall of intraocular pressure, in millimeters of mercury, of 28 normal eyes at time intervals after the administration of 125 mg. of ethoxzolamide.

tients with a marked diurnal variation which would interfere with the interpretation of results. All patients were hospitalized, and after the administration of a single dose of 125 or 250 mg. of ethoxzolamide the intraocular pressure was recorded every 2 to 3 hours for 12 hours. Tonography was carried out between four to five hours after the administration of the drug and was recorded by means of a Mueller electronic tonometer and a Honeywell-Brown recorder. The calculations were corrected for scleral rigidity when this deviated markedly from normal, and the episcleral venous pressure (P_v) was taken to be 11 mm. of Hg.

B. Ethoxzolamide, 125 Mg.—Twenty-eight eyes were tested after the administration of a single dose of 125 mg. of ethoxzolamide. Twenty-five eyes showed a fall in intraocular pressure, whereas three eyes exhibited either no fall or a slight rise after the administration of ethoxzolamide. The average fall, in millimeters of mercury, of the 28 tested eyes at various times after the administration of ethoxzolamide is shown in Figure 1. It can be seen that at two hours the intraocular pressure was somewhat lowered. The fall was maximal at 5 hours, diminished at 7 hours, and almost negligible at 12 hours. The fall of intraocular pressure in millimeters of mercury and also the percentage fall of pressure in each individual eye tested is shown in Figure 2. The average fall in this group was 19%.

C. Ethoxzolamide, 250 Mg.—Twenty-four eyes were studied after the administration of 250 mg. of ethoxzolamide orally. All the eyes showed a fall in the intraocular pressure. The average fall in millimeters of mercury at varying times after the drug is shown in Figure 3. The pressure at two hours was lower than the initial pressure.

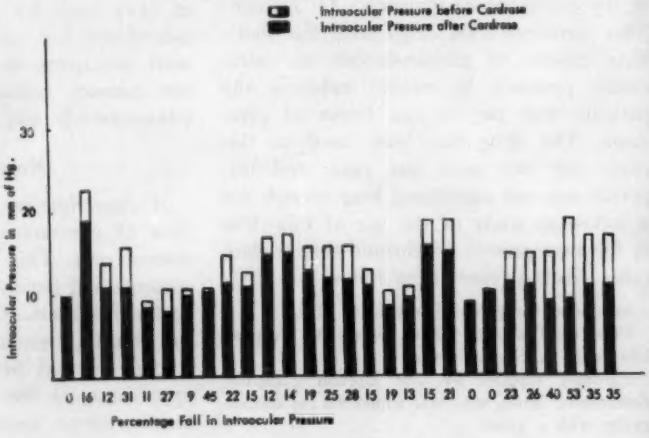
Intraocular Pressure before Cardrase
Intraocular Pressure after Cardrase
Intraocular Pressure in mm of Hg.
10
20
30
0 16 12 31 11 27 9 45 22 15 12 14 19 25 28 15 19 13 15 21 0 0 23 26 40 53 35 35
Percentage Fall in Intraocular Pressure

Fig. 2.—Effect on intraocular pressure in each of 28 normal eyes after 125 mg. of ethoxzolamide. Pressure changes shown in millimeters of mercury and also expressed as percentage changes.

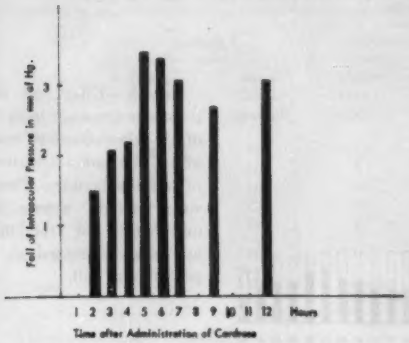

Fig. 3.—Average fall of intraocular pressure, in millimeters of mercury, of 24 normal eyes at time intervals after the administration of 250 mg. of ethoxzolamide.

The maximal fall of intraocular pressure took place five hours after ethoxzolamide administration and gradually decreased after that. It was still well marked 12 hours after administration of the drug. The fall of intraocular pressure in millimeters of mercury and the percentage fall of pressure in the individual eyes tested are shown in Figure 4. The average fall amounted to 27%.

D. Effect on Aqueous Humour Dynamics.

The effect of 125 and 250 mg. of ethoxzolamide on the aqueous humour dynamics in normal eyes is summarized in Table 1. From the results obtained it was evident that ethoxzolamide lowered the intraocular pressure by decreasing the aqueous humour formation by 40% after 125 mg. of ethoxzolamide and by 54% after the administration of 250 mg. of the drug. The aqueous humour dynamics of glaucomatous patients treated with this drug were not reported on because they were much more difficult to interpret, in view of the other forms of therapy which were employed concurrently with the use of ethoxzolamide. It was found that the facility of outflow (C) was not materially altered by the administration of ethoxzolamide.

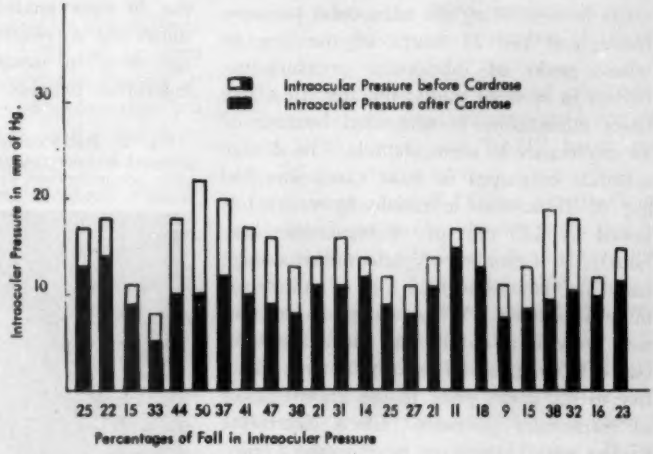
Intraocular Pressure before Cardrase
Intraocular Pressure after Cardrase
Intraocular Pressure in mm of Hg.
30
20
10
25 22 15 33 44 50 37 41 47 38 21 31 14 25 27 21 11 18 9 15 38 32 16 23
Percentages of Fall in Intraocular Pressure

Fig. 4.—Effect on intraocular pressure in each of 24 normal eyes after 250 mg. ethoxzolamide. Pressure changes shown in millimeters of mercury and also expressed as a percentage change.

TABLE 1.—*Effect of Orally Administered Ethoxzolamide on Aqueous Humour Dynamics* *

Dosage	P_1	P_2	C_1	C_2	F_1	F_2	% ΔF
125 Mg.	14.5	12.1	0.22	0.23	0.77	0.25	32.4
250 Mg.	15.0	12.8	0.20	0.2	0.8	0.36	45

* The figures given represent the average values obtained in the study on normal eyes. P_1, P_2 indicate intraocular pressures in millimeters of mercury before and four hours after administration of ethoxzolamide; C_1, C_2, facility of outflow in cubic millimeters per minute per millimeter of mercury before and four hours after ethoxzolamide; F_1, F_2, aqueous flow in cubic millimeters per minute before and four hours after ethoxzolamide; % ΔF, percentage fall of aqueous flow.

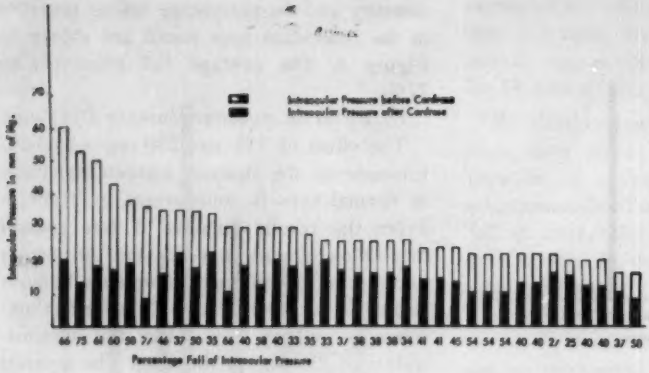
Intraocular Pressure before Cardrase
Intraocular Pressure after Cardrase
Intraocular Pressure in mm. of Hg.
Percentage Fall of Intraocular Pressure

Fig. 5.—Effect on intraocular pressure in each of 36 glaucomatous eyes after the administration of ethoxzolamide. Pressure changes shown in millimeters of mercury and also expressed as a percentage fall.

Glaucomatous Eyes

A. Investigation.—Thirty-six glaucomatous eyes were included in the present study. These comprised 27 eyes with chronic simple glaucoma, 7 eyes with subacute angle-closure glaucoma, 1 eye with secondary glaucoma, and 1 eye with a posttraumatic glaucoma. Ethoxzolamide was used wherever miotic therapy was inadequate in controlling the intraocular pressure throughout the 24 hours of the day or where peaks of intraocular pressure occurred in spite of miotic therapy. In a few cases ethoxzolamide was used because of an intolerance to acetazolamide. The dosage schedule employed in most cases was 250 mg. of ethoxzolamide initially by mouth followed by 125 mg. of ethoxzolamide six-hourly. In a number of patients this dosage could be reduced to 62.5 mg. of ethoxzolamide six-hourly. Whenever peaks of tension were localized by the diurnal tension curve 125 mg. of ethoxzolamide was given five to six hours prior to the known peaks of intraocular pressure. Blood electrolyte studies were carried out prior to the administration of ethoxzolamide therapy and 24 hours after the commencement of ethoxzolamide therapy. These estimations were only carried out on the last few cases included in the study. The drop in intraocular pressure recorded was the maximal drop recorded at equivalent times of day.

B. Results.—All the glaucomatous eyes treated with ethoxzolamide showed a definite fall of the intraocular pressure after the administration of the drug. The fall of pressure varied from 25% to 77% of the initial intraocular pressure. Figure 5 shows the drop of pressure in the individual patients treated, in millimeters of mercury as well as a percentage drop of intraocular pressure. It is to be noted that the average fall of intraocular pressure in the 38 eyes studied was 43%. Figure 6 shows the correlation between the percentage drop in intraocular pressure in the individual patients and their initial intra-

Fig. 6.—Relationship between initial intraocular pressure and percentage fall of intraocular pressure after administration of ethoxzolamide. The correlation is significant at the 1% point.

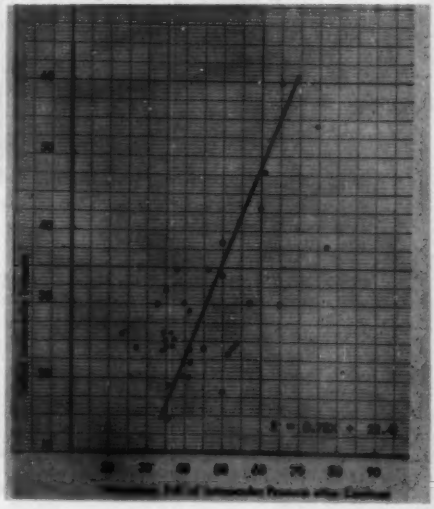

TABLE 2.—*Effect of Ethoxzolamide on Serum Electrolytes in Glaucomatous Patients*

	Sodium *		Potassium *		Chloride *		Bicarbonate †	
Case No.	Before Ethoxzolamide	After Ethoxzolamide	Before Ethoxzolamide	After Ethoxzolamide	Before Ethoxzolamide	After Ethoxzolamide	Before Ethoxzolamide	After Ethoxzolamide
1	140	140	5.2	4.2	105	110	26.5	21.6
2	141	143	4.6	4.8	101.5	111.5	28.8	19.7
3	141	144	4.8	4.9	—	112.6	27	22
4	139	144	5.4	4.5	106.9	115.1	24	19.7
5	140	145	4.7	4.6	105.3	110.1	28.4	25.7
Average	140	144	4.9	4.6	104.6	111.8	26.9	21.7
Change	Increase	2.8%	Decrease	6.1%	Increase	6.4%	Decrease	19.4%

* Values are in mEq/L. serum.
† Values are in mEq/L. plasma.

ocular pressure prior to the commencement of ethoxzolamide. It can be seen that the distribution follows a definite trend which suggests that the higher the intraocular pressure at the commencement of ethoxzolamide therapy the greater the percentage drop in intraocular pressure achieved. This is rather similar to the experience previously reported in the use of acetazolamide in glaucomatous patients.

The electrolyte responses in five patients are recorded in Table 2. It can be seen that there was no appreciable change in the levels of sodium and potassium, but there is a significant fall in the bicarbonate ion concentration averaging 5.1 mEq. (19%). The average chloride ion concentration rose 7.2 mEq. (6.4%).

Side-Effects

The side-effects with ethoxzolamide in the dosage clinically used were slight. Ethoxzolamide, 125 mg., produced only a mild diuresis and paresthesiae of extremities. One patient complained of lightheadedness. Ethoxzolamide, 250 mg., occasionally produced dizziness, headache, anorexia, nausea, and paresthesiae, but in the majority of patients it produced no side-effects at all or only very slight and transient symptoms. Almost all patients had some diuresis which was transient. It must be stressed that these side-effects applied only to short-term therapy with ethoxzolamide, namely, single dosage or therapy for two or three days. It was not intended to report on the side-effects and metabolic effects of ethoxzolamide in long-term cases treated with ethoxzolamide, as this will form part of a subsequent study.

Conclusions

1. Ethoxzolamide lowers the intraocular pressure in normal and glaucomatous eyes.
2. The drop in intraocular pressure was greatest where the initial intraocular pressure was highest prior to the use of ethoxzolamide.
3. A single dose of 125 mg. of ethoxzolamide produced a maximal pressure lowering effect at 5 hours, and by 12 hours the effects were almost entirely worn off.
4. A single dose of 250 mg. of ethoxzolamide produced a considerable reduction in pressure starting before 2 hours, maximal at 5 hours, but still appreciable after 12 hours. With this dose side-effects were noted in some patients.
5. Tonographic studies in normal eyes suggested that the reduction of intraocular pressure with ethoxzolamide was due to an inhibition of aqueous humor formation.

Summary

The effects on the intraocular pressure of a new carbonic anhydrase inhibitor called ethoxzolamide (Cardrase) on normal and glaucomatous eyes are described. Aqueous humour dynamic studies are reported on and toxic effects described. The study

comprised only short-term effects of ethoxzolamide.

Department of Ophthalmology, University of Saskatchewan.

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Postnatal Partial Spontaneous Correction of a Severe Congenital Anomaly of the Anterior Segment of an Eye

A. HAGEDOORN, M.D., and C. M. J. VELZEBOER, M.D., Amsterdam, The Netherlands

On Aug. 7, 1953, a baby was admitted to the Eye Hospital for diagnosis and treatment.

A presumptive diagnosis of buphthalmos had been made by an ophthalmologist, but the unusual aspect of the case led him to ask for further investigation at the University Eye Clinic. He had observed that both corneae were opaque. The right cornea showed a dark area in the center suggestive of a descemetocele. This eye was slightly larger than the left eye. It was impossible to see the iris or the pupil through the gray corneal tissue. In the left eye an atrophic iris could be detected, though with difficulty.

The child had been born on July 8, thus was 30 days old on the day of admission. The mother said she had always been in excellent health and that, while the delivery had been normal, the family physician had immediately told her that there was something wrong with the baby's eyes.

As far as both general and eye diseases or abnormalities were concerned, the family history was completely normal.

A general examination showed the child to be normal and healthy, except for an abnormal fourth toe on each foot and an angioma of the right shoulder. As the condition of the eye was unusual, the examination was made under general anesthesia.

In the right eye the cornea was definitely flatter than normal (cornea plana); its horizontal diameter was 10.5 mm. In the central area the cornea was thinned and dark in appearance, due to translucency. The surface of this area was in line with the rest of the cornea; there was no bulging, as in a descemetocele. This clear central area was surrounded by a white ring. The periphery of the cornea was hazy and considerably thickened so that no details of the interior of the eye could be distinguished.

The left cornea was less opaque, making it possible to observe some particulars of the interior of the eye.

The diameter of the cornea measured 10 mm. horizontally, and the cornea was flatter than normal (cornea plana). In this cornea also there was a central dark (translucent) area surrounded by a dense white ring. The pupil was very large, the iris grayish and apparently atrophic, with a darkly pigmented border suggestive of an "ectropion uveae." In the central dark area of the cornea the lens seemed to be adherent to the posterior surface of the cornea.

On digital examination the tension appeared to be slightly elevated in the right eye and normal in the left eye. Tonometry with the Schiøtz tonometer confirmed this slight difference: R 2 with weight 5 gm. (35 mm. Hg), L 5 with weight 5 gm. (22 mm. Hg). In this case, these figures are of only limited value and too low.

The condition remained rather obscure, and on Aug. 15 an examination was made with slit-lamp microscopy. The central area of the cornea proved to be considerably thinned by a posterior indentation into which the lens fitted; the anterior surface of the lens had become conical or spherical in shape (Fig. 1).

This examination confirmed the fact that there was a very large pupil as well as a definite "ectropion uveae."

These unusual findings were repeatedly corroborated while the baby was in the hos-

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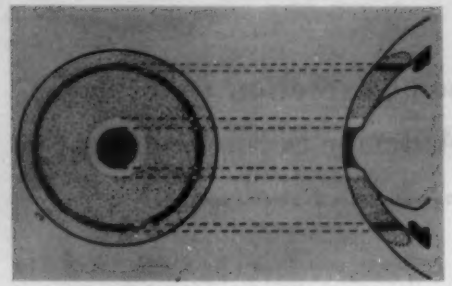


Fig. 1.—Schematic drawing, August, 1953.

pital. It was discharged on Sept. 17. Pilocarpine was prescribed.

The baby was again in the hospital from Oct. 23 to 30. This time examination was much easier; both eyes were held open. There was no blepharospasmus or photophobia.

The right cornea revealed a fundamental change. Instead of being clear, the central part of the cornea which, under superficial examination, had suggested a descemetocele, had become opaque, steamy, and thickened. It was surrounded by a ring-shaped streak, still slightly opaque, but the periphery of the cornea was fairly clear and of normal thickness (Fig. 2).

At the periphery a definite anterior chamber was visible; the iris was atrophic but apparently better developed than that of the left eye. It was not possible to see the lens.

In the left eye the cloudiness of the center was less dense and the periphery more translucent than in the right eye. Since the lens had now resumed its normal position, the anterior chamber of the eye was normal in depth. As the central part of the cornea was opaque, it could not be definitely ascertained whether or not the anterior central part of the lens was normal.

There were slight opacities in the posterior cortex. The iris had broadened a little; the "ectropion uveae" was still present. The baby was in the hospital for the third time from Feb. 22 to 25, 1954.

By overgrowth of the limbus the cornea of the right eye had become oval horizontally. The central opacification of the cornea had decreased in size. There was a central, disciform, intense opacity to be observed in the deep layers, as well as haziness of the whole central area. The epithelium over this area was slightly "glaucomatous"; the periphery was normal. A few tiny radial vessels had entered the cornea. The pupil was much smaller than in the left eye; the depth of the anterior chamber was normal. The anterior layer of the iris was atrophic, exposing the pigmented posterior layer at various points. Radial vessels were seen in the iris.

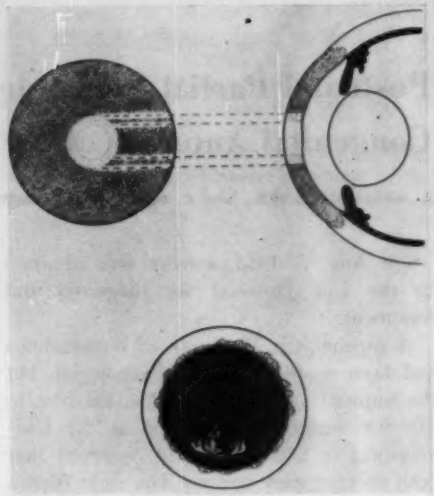


Fig. 2.—Schematic drawing, October, 1953.

In the *left* cornea the central opaque area had also diminished in size; the periphery of the cornea was clear and normal. The pupil was still very large, so that the margin of the lens was visible. There was a well-developed ectropion uveae. The lens appeared undersized and too spherical in shape. There were opafications in the inferior and posterior cortex. Between the margin of the lens and the margin of the iris the fundus could be observed through a narrow slit. There was no red reflex, but there seemed to be a grayish tissue.

The tension of the eyes seemed elevated; the Schiøtz readings were R 3.5/7.5, L

4.5/7.5. In a normal adult eye this would correspond with 53 and 45 mm. mercury, respectively. Treatment with pilocarpine was continued.

The patient was in the hospital for the fourth time from April 22 to May 1. The condition showed a slight improvement. The tension of both eyes had decreased; the Schiøtz tonometer disclosed 38 mm. in both eyes.

A first glimpse of the fundus was obtained.

In the right eye, the disc was small and there was no glaucomatous cupping. In the lower part of the fundus white areas were observed. There was a strand of connective tissue in the vitreous running from the disc region, anteriorly, slightly upwards and toward the temporal side. A vessel could be seen in the tissue. Apparently there was pigment, but this was probably behind the strand in the retina. The central area revealed small white delicately pigmented atrophic fields.

The *left* fundus showed more striking fundamental changes. Here the optic disc was covered by tissue; from this no grayish strand was observed protruding into the vitreous, as in the right eye. Observation was difficult, but apparently there was a detachment of the retina at the temporal side, a vague demarcation line in the retina inferior to the disc, white areas in the superior part of the fundus, and a mass of tissue in the temporoinferior region over which a vessel was seen to pass. At the nasal side grayish tissue and some vessels were seen. It was not possible to give a more accurate description of the fundus.

When the child was readmitted in May, 1955, these findings were confirmed; no red light was reflected from the left fundus. In February, 1956, the right cornea had a more steamy appearance. This made the general outlook more serious, and conservative treatment was abandoned. During the years 1956 and 1957 various operations were performed, after which the tension was digitally only slightly elevated; tonometry gave normal readings. There is still light perception in the right eye—A. V. about 1/300—enabling the child to find its way about.

Comment

There are a number of anomalies in this case which are worth discussing.

A. Cornea.—1. The dark central area suggested a descemetocele (Fig. 1). In a descemetocele Descemet's membrane bulges forward as a transparant bleb surrounded by a ring of opaque tissue. In this particular case, however, the anterior surface of the black area did not protrude.

The dark aspect resulted from a posterior indentation, the transparency being in contrast with the opaque surrounding tissue.

A picture resembling this condition was given by Mans (Fig. 3). It was of an eye removed because of a suspicion of retinoblastoma.

In order to understand the nature of this anomaly a few facts about the normal development of the cornea are of interest.

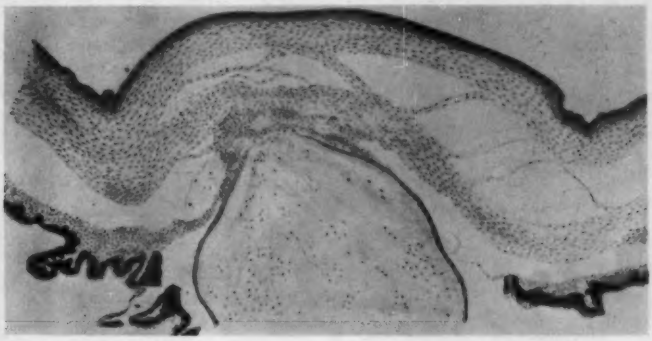


Fig. 3.—Close contact between lens and cornea. Reproduced with permission from Mans: Di Genese der angeborenen Hornhauttrübung, *von Graefes Arch. Ophth.* 119:77, 1928; Berlin, Springer-Verlag.

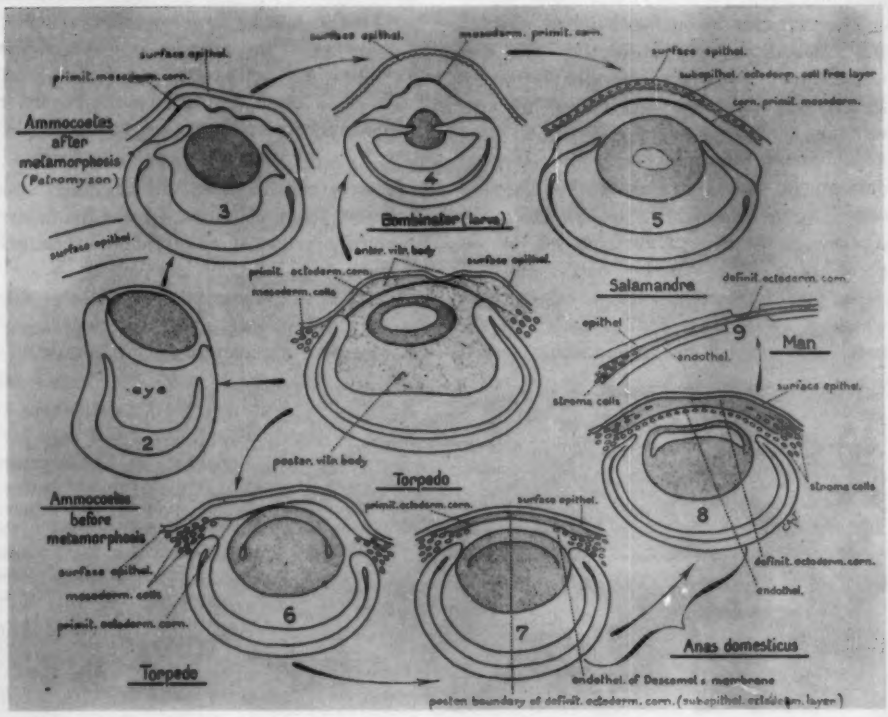
The ultimate construction of the anterior segment of the eye appears to be marked off by directional membranes. In a previous paper in the ARCHIVES it was shown that the potentiality of the eye develops from the "Anlage" in the central nervous system. For the eye to function as an organ of sight a complicated process of adaptation to and integration with the surface ectoderm is necessary, as illustrated in a comparative study of the vertebrate eye in general and the cornea in particular (Fig. 4).

In the Torpedo (a fish) the eye, *sensu strictu*, is marked off anteriorly at a very early stage by a directional membrane, the "cornea primitiva ectodermalis," which develops in the anterior vitreous body (Fig. 5). Occasionally this membrane can be traced in mammals (Tarsius ape).

In certain amphibia this "primitive ectodermal cornea" is reinforced by the ingrowth of mesodermal cells and remains separated from the surface epithelium and its subepithelial layer (Fig. 6). In birds, mammals, and marsupialia, however, the fusion of surface ectoderm and eye is intense from the earliest stages on and the primitive cornea is inseparably fused with the subepithelial layer of the surface epithelium, the "definitive ectodermal cornea" (Fig. 7).

The first mesodermal element of this cornea is the endothelium. The cornea develops further by the ingrowth of mesodermal cells between the primitive ectodermal cornea (not to be confused with Descemet's membrane) and the subepithelial layer of the surface ectoderm. Generally, however, these membranes or condensations are not visible, and the ingrowth proceeds in the thin but resistant definitive ectodermal cornea (Fig. 8).

Fig. 4.—Comparative development of the interior segment of the eye in vertebrates. Reproduced with permission from Hagedoorn, A.: Comparative Anatomy of the Eye, *Arch. Ophth.* 16:783, 1936.



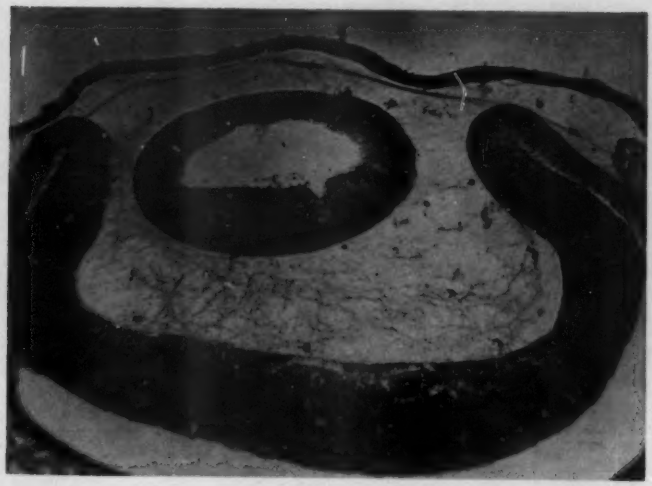


Fig. 5.—Primitive ectodermal cornea developing in the anterior vitreous body in fish. Reproduced with permission from Hagedoorn, A.: Comparative Anatomy of the Eye, *Arch. Ophth.* 16: 783, 1936.

This normal development of the cornea is possible only after the stage in which the lens has been separated from the surface ectoderm. If this latter process has been delayed normal differentiation of the definitive ectodermal cornea in the center is not possible. It may be easily understood that considerable delay in the ingrowth of mesodermal cells in the center of the cornea would result.

A delayed invasion of mesodermal cells in the central area is obviously not compatible with normal translucency. Furthermore, there may have been a delay in the outgrowth of the endothelial layer, which is of fundamental importance for the translucency of the cornea. This explains more fully the absence of Descemet's membrane in the cases cited by Collins and Parsons.

The initial central indentation and the central gray area belong to one syndrome. An appropriate name would be Central Anterior Dysplasia. Keratoconus posticus, either total (Butler) or localized, belongs

Fig. 6. — Eye freely movable under transparent skin (Bombinator). Reproduced from Hagedoorn, A.: Beitrag zur Entwicklungsgeschichte des Auges, *Arch. Augenh.* 102:33-110, 1929-1930.

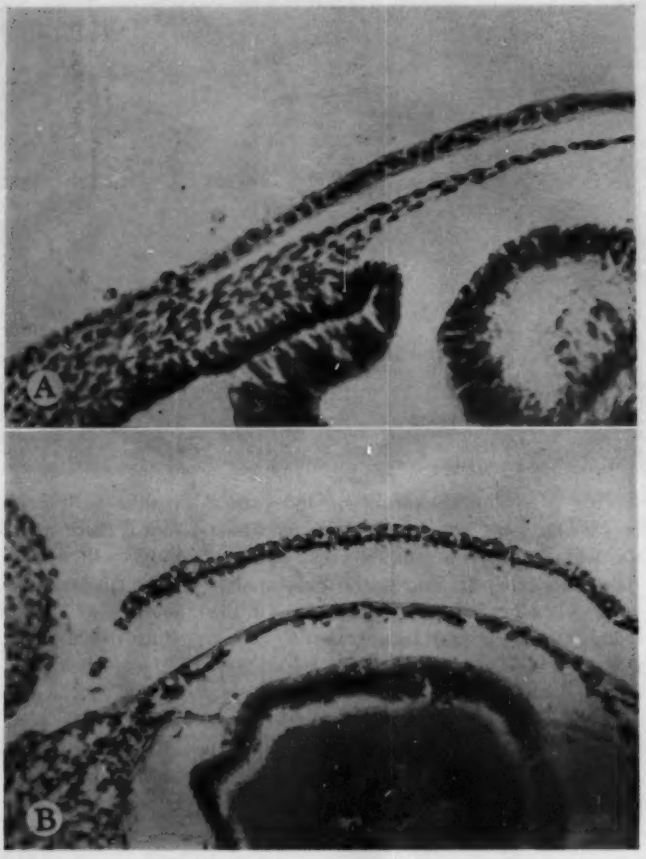
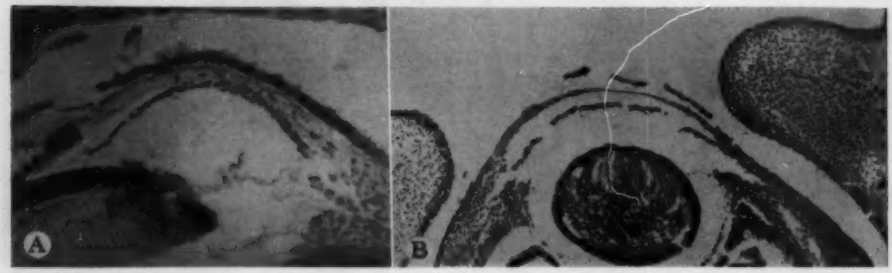


Fig. 7.—*A*, definitive ectodermal cornea, epithelium, and endothelium in marsupials. *B*, definitive ectodermal cornea with epithelium and endothelium in human embryo. Damaged specimen clearly demonstrating the presence of this layer. Reproduced from Hagedoorn, A.: Beitrag zur Entwicklungsgeschichte des Auges, *Arch. Augenh.* 102:33-110, 1929-1930.

to this syndrome. Recently (1957) Jacobs presented a survey of several cases of his own. The pathology of a case has been given by Mans (Fig. 9).

In Fig. 1184 of his book, Duke-Elder gives a picture of a congenital anterior staphyloma, probably a later and more serious manifestation of the same condition.

Fig. 8.—*A*, ingrowth of mesodermal cells in definitive ectodermal cornea in marsupials. *B*, ingrowth of mesodermal cells in definitive ectodermal cornea, epithelium and endothelium attached, in human embryo. Reproduced from Hagedoorn, A.: Beitrag zur Entwicklungsgeschichte des Auges, *Arch. Augenh.* 102:33-110, 1929-1930.



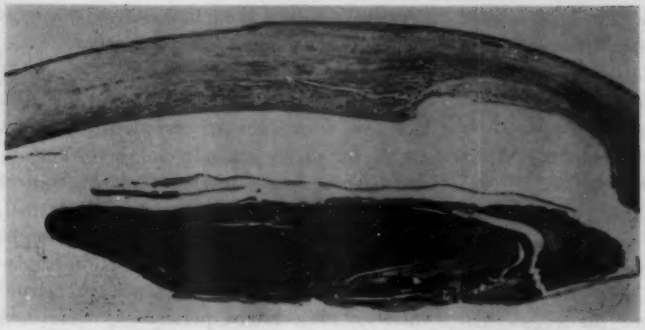


Fig. 9.—Posterior indentation of cornea. Reproduced with permission from Mans: Die Genese der angeborenen Hornhauttrübung, *von Graefes Arch. Ophth.* 119:77, 1928; Berlin Springer-Verlag.

Greene described a localized form of posterior conical cornea. The indentation in the translucent tissue was surrounded by a ring-shaped macula. There were also other abnormalities, e. g., a slight cataract. Greene thought that a delayed separation of the lens vesicle from the surface ectoderm was the probable cause of the anomaly; this is confirmed by our own clinical observation.

2. Since up to the fourth month of life the cornea has the same curvature as the sclera, a cornea plana is a sign of delayed development. Duke-Elder remarked that in these cases the corneoscleral junction tends to lose its sharp definition, the sclera encroaching upon the cornea. In our case this occurred especially at the superior and inferior margins.

B. Lens.—1. The lens was unusual in appearance; it had developed a conical or spherical form that fitted into the posterior indentation of the cornea.

Seefelder and Wolfrum noted a similar lenticonus or lentiglobus in a fetus of four months; this also showed an indentation of the posterior surface of the cornea (Fig. 10).

The pathology of the cornea, lens and iris given by these authors might well be identical with the case presented here. They concluded that the conus is filled with fluid rather than with normal lens tissue.

In Mayou's case, however, the lenticonus contained solid lens tissue, so that the empty space in Seefelder's case might be an artifact due to shrinkage. Duke-Elder noted that persistent anterior lenticonus is a very rare condition. This we can understand, since in our case the lenticonus was completely corrected in the course of a few weeks, though a lentiglobus remained in the left eye.

Fig. 10.—Human fetus (four months), posterior indentation of cornea lentiglobus anterior. 1, More peripheral section; 2, section through the middle of the cornea. Compare with Figure 1. Reproduced with permission from Seefelder and Wolfrum: Über eine eigenartige Linsenanomalie (Lentiglobus anterior) bei einem viermonatlichen menschlichen Fötus, *von Graefes Arch. Ophth.* 65:320, 1907; Berlin, Springer-Verlag.

2. It was observed that the lens seemed to be too small and more spherical than normal. Our case demonstrates that this condition may come from a disturbance of the development of the lens itself, there being no reason for presupposing a primary congenital weakness of the zonule.

C. Iris.—1. The anomaly of the iris may be defined as a *"forme fruste"* of aniridia: brachiridia. In Mans' case "one half of the iris consisted of a short stump only, with development of both the ectodermal and mesodermal layers." In his case and in many others in the literature there was an anterior synechia of the iris with the cornea and glaucoma (buphthalmus).

2. Congenital Ectropion of the Pigment Border: An ectropion in postnatal life has been shown to be due to the traction from shrinking tissue on the anterior surface of the iris. In congenital cases it is to be considered a malformation. In a case of buphthalmus a similar ectropion of the pupillary border was to be observed. It will be recalled that in buphthalmus there is a persistence of embryonal tissue in the angle of the anterior chamber.

Since they were so difficult to observe and identify, it is not possible to discuss the anomalies in the vitreous and retina in our case. Tissue which should have disappeared (arteria hyaloidea) must unquestionably have persisted.

In tabulating the different anomalies and related conditions described in the literature, a number of theories are met with. The main question is the ectodermal or mesodermal nature of the anomaly.

According to experimental embryology it is the eye "Anlage" (optic cup) that makes the surrounding mesoderm instrumental for its purpose.

Experiments with amphibians have demonstrated that the eye "Anlage" causes the surface ectoderm to develop a lens; the lens may even develop directly from the optic cup. It seems logical, therefore, to emphasize the importance of this eye organizer, eye "Anlage," rather than that of the ectoderm or mesoderm.

Any organizing deficiency manifests itself chiefly in two ways: (1) A delay or even lack of formation of ectodermal tissues (with secondary mesodermal involvement) and (2) a delay or even lack of control in the absorption of temporary mesodermal, or mesostromal, tissues. In primary buphthalmus this latter phenomenon is of fundamental pathogenetic importance. A second variety, "mesostroma persistens," described by one of us (A. H.) in these ARCHIVES, seems to be harmless.

A concise survey given by Duke-Elder in the second volume of his treatise deals with the congenital malformations and anomalies of the anterior segment of the eye. There is no necessity for suggesting any other classification. Our case, however, demonstrates the mutual relations of some of these conditions, their individual characteristics, and the limited value of special theories.

Summary

A case in a baby 30 days old with keratoconus posticus, lenticonus, ectopia lentis anterior, and other anomalies is described; in the course of a few months this developed into central corneal opacity, slight microphakia lentiglobus (in normal position). It was associated with partial aniridia (brachiridia), ectropion of the pupillary border, atrophy of the anterior layer of the iris, and anomalies in the posterior segment of the eye. Both feet had an abnormal fourth toe, and there was an angioma of the right shoulder. Subnormal organogenetic potency of the optic cup is considered responsible for the ophthalmological aberration. The normal and abnormal development of the anterior segment of the eye is discussed.

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The Spasticity of Conjugate Gaze Phenomenon

J. LAWTON SMITH, M.D.; ANDREW J. GAY, M.D., and DAVID G. COGAN, M.D., Boston

Lateral conjugate deviation of the eyes on attempted forced closure of the lids was emphasized,[1] in 1948, as a sign of value in the lateralization of cerebral lesions. This finding was termed "spasticity of conjugate gaze" and has also been referred to as the "perverse Bell's phenomenon."[2] The deviation is characteristically to the side opposite the lesion (that is, to the side of hemiparesis and/or hemianopia). Such deviation was noted in only 3 of 156 persons with no known neurologic disease but was seen in 34 of 54 patients with unilateral cerebral disease. It was concluded that spasticity of conjugate gaze is of definite value in lateralizing the lesion. However, this phenomenon has not been analyzed from the point of view of localization within one hemisphere. The present study is an attempt to determine if this test may have localizing significance within one hemisphere, in addition to its already established lateralizing value.

The method of testing employed was to stand directly in front of the patient and, after asking him to close both eyes, to elevate gently one lid at a time and note the position of each eye. Deviation of the eyes either up or up and out on attempted closure was considered a normal Bell's phenomenon in this study. Spasticity of conjugate gaze was present when the eyes consistently deviated to one side (either right or left) on testing several times.

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From the Howe Laboratory of Ophthalmology, Harvard University Medical School, Massachusetts Eye and Ear Infirmary. Special Trainee BT-357, National Institute of Neurological Diseases and Blindness (Dr. Smith), and Heed Fellow in Ophthalmology, Massachusetts Eye and Ear Infirmary (Dr. Gay). Present address of Dr. Smith is 900 Lenton Ave., Baltimore (12).

This report reviews the significance of finding deviation of the eyes on attempted closure of the lids in 145 cases seen in neuro-ophthalmological consultation in the Massachusetts General Hospital during the past year. Of these 145 patients, a normal Bell's phenomenon was noted in 110 cases, and spasticity of conjugate gaze was observed in the other 35 patients. Of the 110 patients with a normal Bell's phenomenon, 44 had intracranial disease with sufficient clinical or anatomic evidence to permit topical localization of the lesion. Of the 35 cases with spasticity of conjugate gaze, 24 had evidence thought sufficient for topical localization of the lesion. The cases with either a normal Bell's phenomenon or with spasticity of conjugate gaze with evidence permitting localization within the cerebrum are as follows:

Lesion Site	Normal Bell's	S.C.G.	% With S.C.G.
Frontal	5	0	0
Temporal	7	5	42
Parietal	4	9	69
Occipital	8	2	20

From these 40 cases with intracerebral localized lesions, spasticity of conjugate gaze (S. C. G.) was most characteristic of parietal lobe disease, occurring in 69% of cases with such lesions. It was also seen with temporal lobe lesions (42%) but was noted only occasionally with occipital lesions (20%) and not at all with frontal lobe lesions. In all but two of these cases, the deviation of the eyes was away from the side of the lesion (i. e., the eyes looked to the side of hemiplegia or hemianopia when these were present). In the two exceptions noted, there was sustained conjugate deviation of the eyes toward the lesion, with a paresis of conjugate gaze to the opposite side.

In the differentiation of posterior and anterior intracranial lesions, the presence of an associated homonymous hemianopia was evaluated. It was found that 19 of 35 patients with intracranial disease and spasticity of conjugate gaze had homonymous hemianopias, an incidence of 54%. However, only 16 of 71 patients with intracranial disease and a normal Bell's phenomenon had concomitant homonymous hemianopias, an incidence of 23%. Long-tract signs were noted in about half the cases with spasticity of conjugate gaze. Thus it is seen that neither hemiplegia nor hemianopia are essential for this phenomenon. In fact, one case (subdural hematoma) showed spasticity of conjugate gaze as the only clinical sign at the onset.

Since the optokinetic response is also reported [3,4] to be of significance in lateralization and localization of cerebral lesions, correlative observations are tabulated for a total of 38 cases with cerebral lesions in which both the optokinetic response and lid closure test were recorded. Cases in which no optokinetic responses were obtained due to amaurosis and cases with brain stem, pituitary, or other lesions with insufficient evidence for localization were omitted from this tabulation. A positive optokinetic nystagmus sign [3] is an absence or marked reduction of the response to targets moving towards the side of the lesion in comparison with movement to the normal side. A negative optokinetic nystagmus sign is a normal, equal, symmetrical response to both sides.

A positive optokinetic nystagmus sign occurred in 4% of patients with intracranial disease and a normal Bell's phenomenon but was noted in 34% of patients with intracranial disease and spasticity of conjugate gaze. It appears that the two signs are significantly but not invariably associated. A positive optokinetic nystagmus sign and spasticity of conjugate gaze tend to be present with parietal lobe lesions but are less frequently seen with temporal and occipital lobe lesions, in that order. Neither was seen with a frontal lobe lesion in this series.

TABLE

	Normal Bell's Phenomenon		Spasticity Conjugate Gaze	
Site Lesion	+ O. N. Sign	− O. N. Sign	+ O. N. Sign	− O. N. Sign
Frontal	0	4	0	0
Temporal	1	6	2	3
Parietal	3	1	9	0
Occipital	1	6	1	1

In addition to the foregoing observations on patients with cerebral lesions, spasticity of conjugate gaze was noted in 2 of 7 patients with pituitary tumors and in 6 of 21 patients with brain-stem lesions. In both instances, spasticity of conjugate gaze was present in somewhat less than one-third of the cases (29%). A negative optokinetic nystagmus sign was found in each of the five patients with pituitary tumor in whom this test had been recorded. A negative optokinetic nystagmus sign was found in 13 of 15 cases with evidence of localized brain-stem disease, with a positive or abnormal optokinetic response noted in but two. However, in the patients with brain-stem disease, evidence for lateralization was not considered sufficiently reliable for interpretation of the optokinetic response.

Summary

Of 145 patients seen in neuro-ophthalmological consultation in whom deviation of the eyes on forced closure of the lids was studied, 106 patients had intracranial disease, and in 68 of the latter group there was sufficient evidence for localization of the lesion. Of 35 patients with intracranial lesions and spasticity of conjugate gaze, 19 (54%) had homonymous hemianopias, and of these 12 had a positive optokinetic nystagmus sign (34% of the cases with spasticity of conjugate gaze). Of 71 patients with intracranial disease and a normal Bell's phenomenon, 16 had homonymous hemianopias (23%), but only 3 of these had a positive optokinetic nystagmus sign

(4% of those with normal Bell's phenomenon).

Of the 68 patients with localized intracranial disease, 44 patients presented a normal Bell's phenomenon and 24 had spasticity of conjugate gaze. Analysis of these patients revealed that spasticity of conjugate gaze was not seen with frontal lobe lesions and was uncommon in occipital lesions. It occurred more frequently with lesions of the midcerebrum, being present in 69% of the cases with parietal lobe lesions and 42% of those with temporal lobe lesions. A positive optokinetic nystagmus sign may occur in brain-stem disease, but there appears to be insufficient evidence to use this test for lateralization in such instances.

Conclusions

Spasticity of conjugate gaze is a rapid test for unilateral intracranial disease, appears to indicate more frequently a lesion of the midcerebrum (parietal and temporal lobes), and is often associated with an abnormal optokinetic response.

243 Charles St. (14).

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Malignant Melanoma of Conjunctiva in Eye of Negro Patient

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In 1941, Anderson [1] examined a series of 14,000 surgical specimens, 78% of which came from Negro patients. Only 10 cases of malignant melanoma arising in American Negroes were among these surgical specimens, and only 1 of these 10 cases was a malignant melanoma of the eye, originating from the retina. In the same series 12 malignant melanomas in various locations were encountered in white patients, pointing to a marked preponderance of these tumors in the white race, as the proportion of white patients in this series was only about 22%.

In 1950, Ash [2] published a report and statistical data on epibulbar tumors based on over 1,000 cases. The proportions of Negro patients approximated 10%, which is also approximately the proportion of Negroes in the total population of the United States. Nevertheless, only 17 Negroes showed conjunctival nevi in comparison to 277 white persons, and only 3 Negroes showed epibulbar malignant melanomas in comparison to 57 white persons.

Callender, Wilder, and Ash [3] examined, in 1942, approximately 1,600 cases of malignant intraocular melanomas (of choroid and ciliary body), but only 8 were diagnosed in Negroes.

Morris and Horn,[4] in a review of the literature on malignant melanomas in Negroes, dispute the marked preponderance of these tumors in white persons. They report nine cases of melanoma in North American Negroes. Only one of these nine melanomas occurred on the conjunctiva (of a 53-year-old woman); all the other eight were in various other nonocular locations. Of the 430 cases of melanoma in African Negroes reviewed by the above authors from the world literature, 287 showed a recorded primary lesion, but out of these only 28 showed a primary tumor in the eye, while 203 were on the lower extremities.

Several authors,[5,6] who described the rather frequent occurrence of malignant melanoma in the African Negro, found the commonest occurrence of the primary lesion on the lower extremities, especially on the sole of the foot, and explained this by trying to prove a relationship between this tumor and exposure to trauma.

On the other hand, Matas [7] feels that in highly pigmented persons the physiological function of pigment formation is under better biological control and the pigment-producing cells thus less liable to uncontrolled growth than in white or lightly pigmented races.

Allen's [8] contention, that nevi on the soles of the feet are almost exclusively of the junctional or precancerous type, would be in accord with Matas' idea, the better biological control of the pigment-producing junction cells in the Negro decreasing their tendency to malignant transformation, thus explaining the scarcity of malignant melanomas in the American Negro and its frequency in the white American, in spite of equal exposure to trauma.

In view of this rather uncommon occurrence of a malignant melanoma in the eye of an American Negro, I feel justified in recording this case, which also has several additional interesting features.

Submitted for publication March 25, 1959.

Department of Pathology, Queens Hospital Center.

Clinical History

A 68-year-old Negro man was admitted on Oct. 6, 1958, to Queens General Hospital with a small, pigmented nodule on the bulbar conjunctiva at the limbus, which was "discovered" by the optometrist about six weeks prior to patient's admission. Patient did not remember noticing "anything" in his eye before.

Past History

The past history revealed hypertension for several years and a cholecystectomy two years previous.

Physical Examination

The physical examination revealed round and equal pupils, which reacted well to light and in accommodation. The left eye showed a pigmented, elevated growth of about 5 mm. in diameter at the temporal limbus, extending for about one-third of its size over the cornea (Fig. 1). Fundus examination showed very small macular changes in the left eye and a normal fundus in the right eye. Slit-lamp examination showed no evidence of iris pathology and no connection with the growth seen at the temporal limbus of the left eye. The other pertinent findings were (1) chronic coronary insufficiency, left heart strain and left ventricular hypertrophy, as evidenced by the EKG, and (2) a 4+ Wasserman and strongly positive VDRL reaction.

Fig. 1.—A pigmented slightly elevated nodule of about 5 mm. in diameter is seen at the temporal limbus of the left eye.

A P^{32} tumor-localization test was performed to aid in the differential diagnosis between a benign nevus and a malignant melanoma. Readings taken over the lesion and over comparison points in the opposite eye showed no significant difference initially and 48 hours after the injection of the P^{32}. On this basis a malignant melanoma was excluded. Nevertheless, it was decided to excise the tumor and submit it to pathology for verification of the diagnosis.

Gross Description of Specimen

Specimen consists of a delicate, membranous fragment of tissue measuring $2\times0.2\times0.1$ cm. It is of white color. In the center a brown nodular elevation is present, measuring about $2\times2\times1$ mm.

Microscopic Description

Section shows tissue from limbus, covered by nonkeratinizing stratified squamous epithelium. The basal layer shows groups of large, vacuolated cells, devoid of cohesion, with prominent, somewhat irregular, hyperchromatic nuclei and fine, dark brown cytoplasmic granules. In several areas these vacuolated cell nests appear to extend upward through the epithelium toward its free edge, thinning the superficial epithelial layer, thus suggesting impending ulceration. In other areas early infiltration of the subepithelial layer is present. Mitotic figures are extremely rare. Acanthosis and epithelial hyperplasia are not prominent. The submucosal layer of the conjunctiva presents groups and nests of large melanophores. A chronic inflammatory exudate is seen at the periphery of the lesion.

Diagnosis

Tissue from limbus: malignant melanoma.

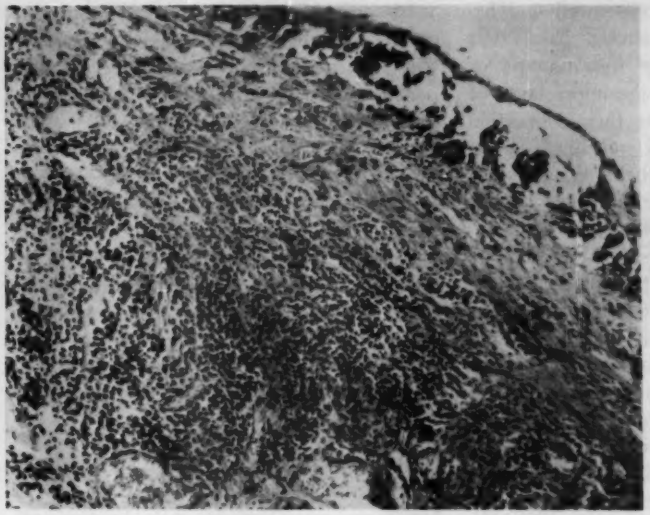

Fig. 2. — Groups of large vacuolated cells, devoid of cohesion, extend upward through the epithelium to its free edge, suggesting impending ulceration. A marked inflammatory reaction is seen in the depth.

In view of this diagnosis the left eye was enucleated on Oct. 15, 1958, and the patient was discharged on Oct. 24.

Comment

In various publications since 1938, Reese [9-11] tried to bring to the attention of the American ophthalmologist, the concept that a malignant melanoma of the conjunctiva usually does not arise from a benign nevus but from a precancerous change in the conjunctiva which parallels a similar change in the skin and which he calls a precancerous melanosis. It manifests itself clinically as a unilateral, asymptomatic, diffuse, nonelevated pigmentation of granular appearance, which may cover large segments of the conjunctiva or even spread to involve the cornea and the adjacent skin of the eyelids. These granular areas may become confluent to form more or less dense sites of pigmentation or widely scattered foci with no apparent continuity. Histologically the basal layer is involved first. Certain cells increase in number and become pigmented and separated from each other by clear

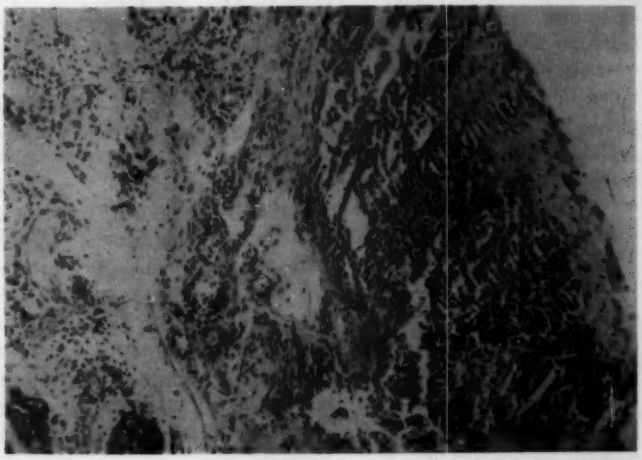

Fig. 3.—Early infiltration of the subepithelial layer by cells with somewhat irregular, hyperchromatic nuclei.

spaces. The individual cells swell and become hydropic. These altered basal cells proliferate and segregate into clumps or nests. They may invade the upper layer of the epithelium after losing their connection with the basal layer, extend towards the free surface of the epithelium, and show more and more anaplastic tendencies. They tend to incite an inflammatory cell infiltration in the subepithelial tissues. When these cell groups penetrate the free surface of the epithelium and invade the subepithelial tissue the cancerous phase is established, and these tumors not only form masses of malignant invading cells but also metastasize to regional lymph nodes and distant organs. The average age at which these changes occur is said to be 40, and the time interval between the first appearance of these changes in the basal layer and their ultimate malignant transformation varies from a few months to a few years. This diffuse melanosis shows a marked tendency to become malignant, although some cases have remained stationary and some have even regressed.

Allen,[8] in his classical monograph on the histiogenesis of cutaneous nevi and melanoma, described the same changes in what he calls junctional nevi. Here too the swelling, vacuolization, and loss of cohesion of single or groups of cells starts in the basal layer of the epidermis. From these groups of altered cells arises the malignant melanoma of the skin by extending slowly up towards the free edge of the epithelium or down into the dermis. Clinically this marginal, junctional or dermoepidermal nevus presents as a smooth, flat, or slightly raised, hairless, light to dark brown macule from several millimeters to several centimeters in diameter and occurs practically on any part of the body, including the conjunctiva. This lesion may be present at birth or may become evident later in life.

Like every malignant melanoma the lesion in our case posed a problem as to its genesis. This resolved itself into whether the lesion arose from (1) a junctional nevus, as described by Allen,[8] or (2) a precancerous melanosis as described by Reese.[9-11] The junctional nevus and precancerous melanosis can be considered as one and the same pathological entity, since and Allen and Reese, despite the use of different terminology describe the same process: in one case (junctional nevus) dealing with a small, well-circumscribed change, in the other case (diffuse melanosis) a more diffuse change in the dermoepidermal junction, both the precursor of the malignant melanoma.

Actually, in the lesion described here, the clinical picture of a small, well-circumscribed macular lesion, as well as the microscopic changes in the basal layer of the conjunctival epithelium and the groups of benign pigment-bearing cells in the subepithelial tissues point towards an origin from a compound nevus.

Another point of interest in this particular case was the failure of the tumor to pick up a significant amount of radioactive phosphorus. This test is based on the fact that malignant tumors have more nucleoprotein and an increased metabolic activity (phosphate turnover) of the nucleoprotein than benign tumors or normal tissues and will therefore take up more P^{32}. This uptake may also depend on the vascularity of the tumor.[12]

Kennedy and Glasser [12] had, in a series of 10 intraocular malignant melanomas, 7 high P^{32} uptakes (initial high uptake, which remained high at the end of 24 hours). The three melanomas of the eye showing a low uptake were small and posteriorly situated.

Bauer and Steffen [13] presented a series of skin tumors, among them several cutaneous malignant melanomas, which showed a definite increased P^{32} uptake in comparison to benign nevi and basal-cell carcinomas. But the authors also point out that increased uptake does not necessarily mean tumor, as infections and granulating wounds which have an increased metabolism may give false-positive results.

Dunphy and Selverstone[14] presented a paper at the New England Ophthalmological Society in November, 1950, in which they cited four cases, which were given intravenous injections of radioactive phosphorus 48 hours prior to enucleation. Malignant melanoma was subsequently found to be present in two; no neoplasm was found in the other two. Still the four cases failed to show any significant difference in the P^{32} uptake between the neoplastic and non-neoplastic tissues.

Schumacher, Schwarz, and Weise[15] presented 6 cases of skin tumors out of a series of 97 cases, which showed 5 false-positive and 1 false-negative result. They also quote an "interesting false negative" found in a series of tests performed by Herzberg.[16] The tumor, a heavily pigmented malignant melanoma, showed histologically no mitotic figures and a low P^{32} uptake. The author assumes that in such cases the mitotic activity and therefore also the metabolic activity is lowered in favor of pigmentation.

Dunphy et al.[17] show another point of importance, namely, that counts taken over malignant tissue may be low initially but tend to increase as time goes by (24 to 48 hours after the P^{32} injections) because tumor tissue tends to retain P^{32} longer than normal tissue. Readings should therefore be taken initially, after 24 hours, and after 48 hours to be conclusive.

In our case there was no significant increase in P^{32} uptake initially or 48 hours after injection. Microscopically almost no mitotic figures were elicited, but the tumor appeared heavily pigmented. Are we therefore dealing here with a metabolic balance between mitotic activity and pigmentation, similar to the case described by Herzberg?[16]

Summary

A case of malignant melanoma, arising apparently from a compound nevus at the limbus in the left eye of a 68-year-old Negro man is presented because of the rare occurrence of these tumors in eyes of American Negroes. The failure of this lesion to pick up P^{32} is also discussed.

The author wishes to thank Dr. Stout for reviewing the slides.

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Annual Reviews

Physiological Chemistry of the Eye

A Review of Papers Published During 1958

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The Cornea

A few papers have appeared during this review period on the subject of corneal composition. Steinvorth and Münich studied the glycoproteins and the lipoproteins of the corneal epithelium.[1,2] They extracted the tissue by grinding with barbital (Veronal) buffer and did paper electrophoresis on the supernatant solutions. At the end of a 14-hour period, the paper was stained for lipoprotein with Sudan black. After the location of the dyed bands, the paper was decolorized once more with organic solvent. It was then cut in half longitudinally. Half of the strip was stained for protein with amino black 10B. The other strip was stained for glycoprotein by toluidine blue after pretreatment with periodic acid and bromine water. Corneal epithelium produced four distinct peaks of glycoprotein and two peaks representing lipoprotein. The two latter seemed to correspond to two fractions of serum when the corneal extract and serum were run in parallel fashion. However, neither sets of proteins were further identified.

A histochemical study by Dark[3] had a somewhat similar objective. This author stained sections with Sudan black-B to demonstrate lipids and used Baker's acid-hematein method for phospholipids with use of pyridine-extracted sections as controls. He was able to demonstrate a rich accumulation of phospholipid in the corneal epithelium, endothelium, and stromal cells. Further, the tonofibrils and intercellular bridges in corneal epithelium were shown to contain phospholipids.

In a further contribution on acid mucopolysaccharides, Hoffman, Linker, and Meyer[4] reported their deductions on the location of the sulfate linkage in the three chondroitin sulfates, designated A, B, and C. Evidence is adduced to show that A and C are identical after desulfation. These substances behave identically in regard to hyaluronidase, have similar absorption spectra, and are similar to corneal chondroitin. The authors had previously isolated chondrosin in high yield from chondroitin sulfates A and C and identified it as β-3 glucuronosyl galactosamine. Thus A and C must differ only in position of the sulfate linkage. Since previous work identified the location of the sulfate in chondroitin sulfate-B as the 4 position, the known identity of sulfate linkage must make A a C-4 sulfate. Since C-6 is the only other free position, chondroitin sulfate C, according to the authors, must be a C-6 sulfate.

A number of papers appeared which were oriented toward studies of corneal grafts or healing of nonspecific corneal wounds. A number of these studies used S^{35} as the chief analytical tool. In a report by Dohlman,[5] rabbits were fed radioactive sulfate until corneas had received a significant amount of label, and corneal transplants were performed with the cornea of the labeled eye as donor. In two weeks' time the isotope content of the grafted eye rapidly decreased to one-third of the value in the control eye of the donor animal. The

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loss after this period was the same both in the transplanted and in the control eye. The author attributed the first rapid decrease to loss of the limiting layers and the later phase to substitution of the ground substance by the host animal. When S^{35} was given to an animal after a graft had been performed, there was considerable S^{35} uptake at the wound edges during the second and third postoperative week, and this uptake was proportional to the amount of fibroblast proliferation. The tacit assumption here is that the labeled sulfur is predominantly a tracer for sulfated mucopolysaccharides.

A study by Dunnington and Smelser[6] dealt with the incorporation of labeled sulfur into the healing portion of a rabbit cornea which had been subjected to a 2 mm. long perforating incision. Differences were observed between untreated corneas and those which had been momentarily frozen by a dry-ice applicator just before incision. Animals were killed 1 to 22 days after this procedure, and seven hours before autopsy they were given 1 mc. per kilogram of labeled sulfate intravenously. Radioautographs were made by the painted emulsion technique, and the amount of density in the radioautograph was considered by the authors a legitimate measure of mucopolysaccharide synthesis. As early as the 17th to 24th hour, an increase of S^{35} incorporation could be detected at the wound edge. This even preceded formation of the argyrophilic reticular fibers. Further events in the normal cornea follow the description of Weimar,[7] who observed marked incorporation of S^{35} in the wound area on the fifth and sixth day. The area of radioactivity corresponds exactly to the area of new connective tissue. By the 22d day the rate of S^{35} incorporation, although higher than the surrounding area, had become less intense than previously. In the frozen corneas examined by the authors, early recovery from the lesion is uneven and ability to synthesize S^{35} polysaccharide is nonuniform over the wound. However, by the 15th day the rate of synthesis had become nearly normal.

In the course of the discussion, the authors mentioned unpublished data of Smelser, Copenhaver, and Queensberry which has considerable interest. These authors, with use of the same technique of injection of S^{35}-labeled sulfate and subsequent radioautography, found that once the sulfur was incorporated into corneal mucopolysaccharides the content was essentially stable for at least 24 days—the period of the experiment. However, in contrast, there was a rapid turnover in the sclera at a rate comparable to that found in the large arteries. This would seem to be a notable difference between two tissues whose composition is similar in so many respects and whose over-all metabolic activities are in inverse proportion to the turnover rate described here. A similar finding was reported by Dohlman (1957).

A report of Nemetz,[8] although with use of less precise analytical methods, also bears on the problem of corneas for transplant. Using human eye-bank corneas, this worker compared fresh specimens with those stored in paraffin oil for 5 to 10 days. He noticed a decrease in basophilia toward methylene blue and a marked decrease in swelling capacity. By 48 hours fresh corneas stored in Ringer's solution increased in weight 30% to 80%; corneas stored 30 days under oil took on only 20% of their weight in water and then gained no more. Curiously, the difference was even more accentuated if the cornea had been preserved attached to a ring of sclera. By 10 days in storage the epithelium and endothelium had disappeared and the nuclei of the stroma were shrunken. The parenchyma had become less stainable with PAS and alcian blue.

A few additional studies appeared on corneal permeability, transparency, and thickness. One of the reports in this category by Coulombre and Coulombre[9] represents a continuation of the work of these two authors on the development of the

cornea in the embryo chick. In the present communication they studied rate of hydration when corneas were immersed in distilled water and compared this rate of hydration to the change in transparency. This was measured by the change in transmission of a narrow beam of collimated light passing through the cornea, falling on a photocell, and recorded by a continuous recorder. Corneas were studied on the 9th to 21st days of incubation and showed rapid water uptake, with the maximum reached at about 60 minutes. Corneas imbibed from 2 to 4.5 times their initial weight in water. However, the degree of hydratability decreased during the time period investigated, and 9-day corneas could imbibe 2.5 to 4.5 times as much water as 21-day corneas. The authors described as the result of previous studies how the cornea begins to establish its stromal collagen pattern on about the 8th day, how the cornea begins to dehydrate on about the 9th day, and how metachromatic mucopolysaccharide appears on the 14th day, at which time transparency begins and dehydration accelerates. At least some of this change must be attributed, on the basis of the findings reported, to change in water-binding capacity of the corneal constituents. Further, when transparency was measured during the course of hydration it was found that at all measurement periods when the cornea was immersed in distilled water, there was a rapid decrease in transparency over the first six or so minutes. By this time virtually all of the loss in transparency occurred and half or less of the total hydration had taken place. As the authors recognized and as was pointed out in the discussion, this lack of parallelism may represent hydration behavior of the various substructures of the cornea in a manner similar to that found for the beef eye.

A report on corneal permeability changes by Gligoriejevic and co-workers also appeared during this period.[10] These authors used a quartz generator which put out energy at 800 kilocycles and 0.5-3 watts per square centimeter. The radiation was transmitted to the cornea by means of a lucite cylinder attached to the diaphragm of the ultrasonic generator and containing in its other end a concavity to fit the cornea. Intensities transmitted to the cornea were 0.2-1.5 watts per cm. sq. The authors used a solution of I^{131} in saline for the cornea during a five-minute exposure or applied it to the cornea immediately after the exposure. The right eye was used for irradiation; the left eye was treated in the same way except that the instrument was not turned on. The authors concluded that irradiation with ultrasound for the period of time described markedly increased the permeability of the cornea to I^{131}.

A further contribution to corneal permeability and water movement was made by Beswick, Langley, and McCulloch.[11] These authors observed the transport of fluorescein through the cornea either from the anterior to posterior direction when a 20% solution was applied to the epithelial surface in applicator or from the posterior to anterior direction when 50 cu. mm. of a 20% solution was injected into the anterior chamber (by means of a special manometer-connected side-entering needle which allowed injection without change in intraocular pressure). The experimental animals were rabbits under pentobarbital (Nembutal) anesthesia, and the end-point was determined by slit-lamp observation and occurred when fluorescein ran down the endothelial or epithelial surface after being applied to the opposite surface. The assumption is made in interpreting all data that fluorescein, being a relatively polar substance, actually is an indicator for the movement of fluid through the eye in either direction. The findings that abrasion of epithelium facilitated anterior to posterior penetration and that abrasion of endothelium facilitated posterior to anterior penetration were perhaps not surprising. A truly unique finding was that when the dye was applied to the posterior surface and a

limited area of cornea was abraded, penetration of fluid under the abraded area was distinctly less rapid from posterior to anterior direction than the fluid flow under the still intact corneal epithelium. These findings led the authors to postulate an active role for epithelium in conveying fluid from the posterior to anterior direction and the endothelium in conveying fluid from the anterior to posterior direction. Experiments on change in intraocular pressure suggested that this latter activity is counteracted in part by the intraocular pressure tending to force fluid from posterior to anterior.

A single note on metabolism of the cornea appeared in the abstracts of the XVIII International Congress of Ophthalmology by Kurachi,[12] describing a study on the metabolism of the cornea in a 7-month live-born fetus in comparison to the adult. It was found that the Q_{o_2} of cornea was higher in the 7-month fetus than in the adult and that the Q_{o_2} of isolated cornea was maintained well for a period of 18 hours when the cornea was preserved at 5 C. A decrease of the corneal Q_{o_2} was observed in vitamin-A-deficient rabbits.

A carefully executed histochemical study on developing rat cornea was reported by Kuhlman and Resnick.[13] These authors used the microtechniques of Lowry which had been previously applied to brain and to retina. The technique involves making frozen sections of the tissue in question, drying the sections while in the frozen state, performing microdissection to separate a sufficient mass of the type of cell desired, weighing this mass on a quartz fiber microbalance, and determining enzyme activity on a microscale by methods which are specific for each enzyme activity in question. The authors of the present study investigated the eye of the rat at birth and at 10, 20, and 100 days thereafter. They assayed for hexokinase, aldolase, lactic dehydrogenase, isocitric dehydrogenase, glucose-6-phosphate dehydrogenase, and glutamic dehydrogenase. Perhaps the most striking finding was the high level of lactic dehydrogenase found in corneal epithelium. When the measurement was made in the direction of lactic formation, the authors found 77 moles per kilogram of dry tissue per hour of substrate acted upon, and when the adult rabbit and the cat were investigated, these yielded figures of 1,500 and 103, respectively. In general, for all enzyme activities, the corneal epithelium increases until the 20th day, at which time a plateau is reached. Conversely, in the corneal stroma the activity of all enzymes per unit weight decreases with age. These changes parallel an increase in the relative number and mass of nucleated cells in the epithelium and a decrease in the number and relative mass of such cells in the stroma. The authors considered the activity of the glucose-6-phosphate dehydrogenase as a possible measure of the proportion of activity by way of the direct oxidative pathway and the activity of aldolase as a possible measure of activity via the Embden-Meyerhof pathway, and they examined the ratios of these two activities for epithelium and stroma. They found an increase in the ratio from 3 to 5.8—the direct oxidation being increasingly more significant. Conversely, this ratio decreased for corneal stroma. Isocitric dehydrogenase levels were found to be greater than those of glucose-6-phosphate dehydrogenase in the epithelium, and this led the authors to suggest that the citric acid cycle may play a more significant role in metabolism of the epithelium than credited to it by Kinoshita and Masurat (1954). The authors appreciated, however, that for such conclusions to be valid one must actually be comparing enzyme activities which are truly rate-limiting, and this type of conclusion must be reached from several different approaches to have rigorous validity. Activities of hexokinase and aldolase were generally far below those of the enzymes previously mentioned. The writers believed that this confirms the work of Green and co-workers (1955), who considered hexokinase to

be a limiting step in lens and corneal metabolism. The authors suggested that aldolase is a second limiting step in the glycolitic scheme. Also hexokinase and aldolase do not increase in corneal epithelium from the newborn levels. It was suggested that this may represent a decrease of glycolysis relative to the increase in the shunt mechanism.

The Aqueous

Significant among papers on the aqueous during 1958 was a comprehensive review published by Langham.[14] The reviewer noted a recent shift in emphasis from study of blood-aqueous permeability to the problem of the control of the intraocular pressure, presumably stimulated by recent clinical studies. These have shown that increase in resistance to outflow is typical of clinical glaucoma and that glaucoma therapy depends either on modification of aqueous formation or of its outflow.

Langham treated the subject of the aqueous under three chief headings, the first of which deals with the formation and circulation of the aqueous humor. This subject in turn he considered under three subheadings, the first of which is intraocular dynamics. He reviewed the evolution of the mathematical formulation for the behavior of substances passing from blood to posterior chamber to anterior chamber. Later the behavior of specific substances, the monosaccharides, ascorbic acid, and water, are considered in detail.

Under a second subheading Langham discussed the role of carbonic anhydrase in secretion of the aqueous humor and the numerous studies done with carbonic anhydrase inhibitors—an area still replete with unresolved problems.

Under a third subheading, the reviewer discussed the thermodynamic equilibration between aqueous humor and plasma. He rejected the differences found in osmotic pressure between these two fluids both by direct measurement and by measurement of change after dialysis as probably being due to methodological error. He suggested that the bulk of the aqueous humor is in osmotic equilibrium with the blood.

Under a second major heading Langham discussed the mechanism of drainage of fluid from the eye. He discussed the anatomy of the outflow channels, the recent studies of the effects of hyaluronidase on outflow, and the question of the site of major resistance to aqueous outflow.

In the third major section the reviewer discussed regulation of the intraocular pressure. In this section are discussed articles on the influence of pressure on formation and drainage of aqueous humor, the function of central and peripheral nerve activity, and the nature of the stimulus to the homeostatic process. Certainly this review represents a satisfactory point of departure for anyone desiring current information on problems and accomplishments in this field.

Of the original papers on the subject of the aqueous humor, a number dealt with various aspects of the composition of the aqueous, and of these several were concerned with the protein content. François, Rabaey, and Evens [15] reported on a method of agar microelectrophoresis of the aqueous which required only 25μl. to 80μl. of aqueous for its performance. Thus, from an anterior chamber puncture of 100μl. to 150μl. one could have material for the electrophoresis plus enough for additional microdeterminations. The method described by these authors involved removing salts by dialysis and concentrating by lyophilization. Electrophoresis was done in an agar layer 1.5 to 2 mm. thick on a microscope slide. A current of 8 to 12 ma. was allowed to flow for 10 to 30 minutes. At the end of the experimental period, the slide was fixed in acetic acid ethanol, dried at 37 C, stained with amino black 10B, decolorized in 5% acetic acid, and dried. After clearing in toluene the slide was mounted in resin and the bands were read in a densitometer—the resultant curves being plotted on paper. Integration by planim-

eter or by weighing the cut-out curve gave total amount of protein in each electrophoretic band.

The authors compared results on aqueous with those on serum and cerebrospinal fluid controls. It was found in the course of these investigations that γ-globulin stains less intensely than a corresponding weight of albumin, and a correction factor of 1.85 had to be introduced for the γ-globulin. Preliminary experiments on normal human aqueous showed that the albumin was in greater proportion and the γ-globulin in smaller proportion than the corresponding serum. A prealbumin peak is found in the aqueous as it is in cerebrospinal fluid. The proportion of α-globulin can be either greater or less than the corresponding serum, whereas the β-globulin is the most consistent and corresponds in proportion to serum drawn at the same time.

A report in a similar vein is that of Forsius,[16] who used paper electrophoresis to determine proteins in the aqueous humor of enucleated eyes. Determinations were done on 44 eyes enucleated for various diseases from traumatic uveitis to absolute glaucoma. Electrophoresis was done on paper, and protein was stained with amino black 10B. The density was measured photometrically, and areas under density curves were integrated by planimetry. The author reported figures for α-1-, α-2-, β-, and γ-globulins and for albumin. However, since numbers of these determinations were done on hypopyon eyes and on bloody intraocular fluids, the significance of these determinations for chemical pathology is subject to some conjecture.

In a somewhat different direction is the immunoelectrophoresis study reported by Dubler and Scheidegger.[17] With use of a method previously described by Scheidegger in 1955, the authors placed several antisera in gelatin blocks and had the proteins of the aqueous sample migrate toward the antisera under the influence of an electric potential. The results were rings of precipitin reaction dependent on the rate of migration of the protein fraction and its antigenicity versus the antiserum. No quantitative results were reported. However, the authors had the impression that in iritis the γ-globulin of the aqueous is not elevated in proportion to that in the serum.

In yet another paper on the presence of a protein in the anterior chamber, Langley and McCulloch[18] demonstrated by means of the standard Ostwald viscosimeter that the viscosity of a vitreous filtrate is not altered by addition of an aqueous sample. With use of material from beef eyes as a control it was demonstrated that with a known active preparation of hyaluronidase the viscosity of the vitreous filtrate could be reduced to that of isotonic saline. Hence the authors concluded that aqueous of the beef eye contains no hyaluronidase. This, they point out is doubly significant for the aqueous humor because it makes it theoretically possible for the trabecular meshwork to contain hyaluronic acid, as postulated by Bárány (1955), without its continuous erosion by aqueous enzyme.

Another study by Giles and Harris[19] deals with insulin levels in the aqueous. The insulin was labeled with I^{131}, and its content in the aqueous was determined by precipitation with trichloroacetic acid and determination of radioactivity on the precipitate. On the basis of various control experiments concerned with migration on paper with carrier insulin and with carrier plasma albumin, the authors concluded that insulin in the aqueous reaches a maximum 45 minutes after intravenous injection and at this time reaches only 1/100 the plasma level. The authors concluded that this low level precludes the direct action of insulin on the lens.

Hückel[20] investigated how withdrawal of aqueous from one eye affected the protein content of the aqueous of the other eye. He used a dye precipitation determination with acetic acid and a methanol solution of amino black 10B. The precipitate was

washed, dissolved in base, and read in the colorimeter. The author found that when the second eye was punctured at varying intervals after the first eye was drained, the protein of the second eye aqueous fell to about 50% of that of the first eye and that this drop lasted from three to nine hours. He was unable to adduce a physiological explanation for this finding.

Protein content of the aqueous in eye disease was studied by Remky,[21] who reported his results on 40 cases of uveitis. He measured total aqueous protein with an amino black micromethod comparable to that just described and compared findings with those of serum. To separate individual proteins he performed paper electrophoresis. This author stated that the albumin in the anterior chamber does not reflect the level in the serum and hence is actively transported. However, according to Remky, globulins do reflect the serum level. Nevertheless, on the basis of his determinations he was not able to demonstrate diagnostic significance for his aqueous protein determination.

Moreau[22] reported on the proteins of the aqueous in chronic simple glaucoma obtained by anterior chamber puncture and separated by electrophoresis. In chronic simple glaucoma this author found the albumin to be lower and the globulin higher than in the normal subject, and he postulated a theory according to which loss of protein from the anterior chamber is determined by the size of the outflow channels which selectively retain large molecules. This would require a pore size of outflow channel at least a whole order of magnitude smaller than the half-micron which is becoming generally accepted today.

A few reports dealt with other components of the aqueous. Auricchio and Wistrand[23] described the chloride content of the aqueous during unilateral horse serum uveitis in the rabbit. They tapped the inflamed eye and the control eye under aprobarbital (Numal) anesthesia 30 minutes after heparinization. The chloride ion content was determined potentiometrically. The normal eyes averaged 107.7 mEq. per liter ± 20, a figure comparable to normal values obtained by others. The uveitis eyes averaged 0.920 ± 0.108, which is significantly different and perhaps not surprising in view of the necessary alterations in the blood-aqueous barrier caused by the inflammatory process.

The oxygen content of the anterior chamber aqueous of the anesthetized rabbit was investigated by Drenckhahn and Lorenzen[24] by a polarimetric method comparable to that reported by Heald and Langham (1956). The present authors used a platinum electrode in the anterior chamber and a calomel reference electrode in a saline pool in the cul de sac. They found pO_2 equal to 21 to 46 mm. of mercury, compared to 26 to 80 for Heald and Langham. When the animals were allowed to breathe pure oxygen, there was a rapid rise to saturation in 20 to 25 minutes. On stopping oxygen, the oxygen content fell to an asymptotic value in the same period of time. The authors concluded from this that the solubility of oxygen in the aqueous is the limiting factor in the oxygen content of the aqueous humor.

Another series of papers had bearing on the mechanism of aqueous formation by investigating the content of inorganic ions, the osmotic pressure, or the influence of carbonic anhydrase inhibitors on aqueous composition. In this category is a report by Kinsey and Palm on the penetration of sodium and thiocyanate into the posterior and anterior chambers.[25] This is essentially the recalculation of the data presented by these authors in an earlier paper (Kinsey and Palm, 1950). Correction has been made for the amount of thiocyanate bound to plasma protein, a factor not considered in the previous paper and criticized by Davson. Curves were fitted for the recalculated data, and transfer coefficients were calculated. The data were found to be consistent with a flow rate of 1% to 1.25% per minute, or, in Kinsey's transfer equa-

tions, a flow constant of 0.010 to 0.0125. The authors stated that from these recalculated data, too, the most logical assumption is that sodium enters the posterior chamber by secretion, but that thiocyanate is subject to a two-way process; that is, diffusion. They also consider their results consistent with the hypothesis that both sodium and thiocyanate enter the anterior chamber by flow from the posterior chamber and by diffusion across the iris-aqueous barrier. Both ions are believed to leave the anterior chamber by flow and by back diffusion.

Another paper bearing on the mechanism of aqueous formation is that of Levene.[26] This author repeated the experiment of Duke-Elder and co-workers, in 1949, in which the question of aqueous as a secretion was approached by dialyzing aqueous against plasma, measuring concentrations of each before and after dialysis, and ascertaining whether a difference in concentration of each was detectable as a result of the dialysis. The finding of such a difference was interpreted by the earlier workers as indicating that aqueous was secreted by an energy-utilizing process. In the present set of experiments, the aqueous from seven rabbits representing 1.5 ml., was dialyzed across a cellulose membrane against a volume of plasma 10 times as great. Sodium and potassium were measured by flame photometer and osmolarity was determined by freezing-point depression with the Fiske osmometer on a 0.2 ml. sample. The results confirmed the earlier report that there is an excess of sodium ion in the aqueous. However, Levene presented evidence that the sodium excess is balanced by a deficiency of other substances so that there is no great difference in osmolarity of aqueous and plasma. The author suggested that these results do not favor the primary transport of bicarbonate followed by secondary transfer of sodium ion, because the potassium ion has a greater mobility than the sodium ion. If one were dealing with secondary diffusion, one would expect the more mobile cation to be the one present in the aqueous in higher concentration.

A report by Green, Mann, and Paul concerns itself with the contribution of the lens to the bicarbonate content of the aqueous humor of the rabbit.[27] In a series of rabbits, these authors produced monocular cataracts by massaging the anterior lens surface with an iris-repositor through a small incision; in other animals, they created a monocularly aphakic animal by performing extracapsular extraction of the lens. In the cataractous eye, they found no change of bicarbonate concentration or pH in comparison with the contralateral control eye. In the aphakic eye, the pH was found to be unchanged, but the bicarbonate concentration of the anterior chamber was 8% less and in the posterior chamber 13% less than in the control. This anterior chamber difference represented 7% of the total bicarbonate and 22% of the excess of bicarbonate over the blood plasma level. The difference in the posterior chamber represented 11% of the total bicarbonate of the aqueous and 25% of the excess aqueous concentration over that of the blood plasma. In discussing these results, the authors stated that one cannot account for this quantity of bicarbonate by the lens production of CO_2. As an alternative, it is suggested that active transport of bicarbonate ion into the posterior chamber is stimulated by elaboration of lactic acid by the normally metabolizing lens and that in the absence of this stimulation the bicarbonate concentration in the posterior chamber is significantly decreased.

Of the several papers dealing with carbonic anhydrase inhibitors, one involved measurement of osmolarity in the dog and rabbit as a result of acetazolamide injection.[28] For these experiments, Levene used the restrained, conscious animal with topical tetracaine (Pontocaine) anesthesia. The aqueous puncture for the control eye was made in the right eye, and five days later, after administration of acetazolamide (Diamox), aqueous was collected from the left eye. Results obtained by freezing-point depression measurement with the Fiske osmometer showed, for rabbits, an aqueous

concentration of 300.6 mOsm. per kilogram and for plasma, 298.5 mOsm. per kilogram, a difference of only 2.1 mOsm. Two-and-one-half hours after injection of acetazolamide, there was a parallel decrease in the osmolar concentration of both aqueous and plasma. As the author pointed out, even though statistical analysis yields a standard error of the difference of means of 0.6% to 0.7% of the normal osmolar concentration, this may be misleading, for an osmolar change of more than twice this error may be biologically significant. He also points out that the presence of a measurable aqueous-to-plasma osmolar gradient is not necessary for net fluid transfer across the blood-aqueous barrier. If the ease of water transfer were much greater than that of solute transfer, the secretion of an osmotically active particle would be immediately followed by an associated osmotic transfer of water, even though no measurable steady-state osmotic gradient could be demonstrated.

In still another paper, Levene[29] described sodium and potassium concentration changes in the same animals treated with acetazolamide. He found that 30 minutes after administration of the drug, there was a small but equal decrease in the concentration of potassium in aqueous and plasma, and that this was significantly greater than in animals given a control injection of isotonic saline. There was no effect on sodium concentrations detectable. However, since for the flame-photometer determination used the standard error of the difference of the means for sodium was 1.3% of the normal sodium concentration, the author stated that a physiologically significant change might well escape detection. On other grounds, too, the author still favored active transport of the sodium ion as the primary mechanism in aqueous formation.

A newer carbonic anhydrase inhibitor, dichlorphenamide (Daranide) figures in a report by Tanner and Harris,[30] who measured freezing-point depression in the Fiske osmometer for rabbit aqueous before and after administration of the drug. The authors found the mean value for the aqueous to be equivalent to 294.3 mOsm. for the rabbit, with a mean aqueous-plasma difference of 1.76. The figures for the cat were 316.5, with a difference of 2.10. No change in these values was observed after administration of dichlorphenamide or dibenamine, an adrenergic-blocking agent—both substances known to lower intraocular pressure. Under osmotic stress, with the plasma made hypertonic by intravenous glucose or saline or made hypotonic by intraperitoneal injection of hypotonic glucose, the cat still showed no measurable change in osmotic pressure of aqueous. The rabbit was more labile, however, and aqueous tended to follow the plasma osmotic pressure, the change being two-thirds that of the plasma change.

A bit of research not directly on the eye but of significance because it deals with a side-effect of an carbonic anhydrase inhibitor was reported by Shah, Constant, and Becker.[31] It has been recognized that persons receiving acetazolamide at dosage levels used for glaucoma are prone to formation of renal calculi, chiefly of calcium oxalate (Persky and co-workers, 1956). Previous experimental and clinical work had suggested a role for citrate in chelation, and hence solubilization of urinary calcium, and had indicated a decrease of citric excretion in experimental animals treated with carbonic anhydrase inhibitors. The present report concerning 24-hour urinary citrate excretion before and just after 250 mg. of acetazolamide showed a mean decrease of citrate excretion of 62% without corresponding decrease of calcium ion excretion. Patients on long-term acetazolamide treatment showed a mean citrate value of only 10% to 15% of the normal, and patients with renal colic showed similarly decreased citrate excretion. However, no difference could be demonstrated in the urinary citrate of the colic patients compared to the noncolic patients.

One report by Auricchio[32] concerned the osmotic pressure of the aqueous during experimental uveitis in the rabbit. In these experiments rabbits were sensitized to horse serum by intravitreous injection and shocked 10 days later by an intravenous dose of horse serum. When the osmotic pressure of the aqueous was examined by the vapor-pressure technique of Hill and Baldes, there was a consistent decrease of the aqueous osmotic pressure in the diseased eye, although no difference was observable between anterior and posterior chambers. The question arises whether this effect is a reflection of a decrease in aqueous secretion.

The Uvea

One of the few publications on the biochemistry of the uveal tract was that of Waitzman and Ballintine on the adenylic acid deaminase activity of ciliary processes.[33] These authors described an enzyme present in extracts or homogenates of ciliary processes from hog or rabbit which is able to deaminate adenosine-5-phosphate and which has no activity versus the 3-phosphate. The enzyme worked most effectively when ATP or ADP were present in equimolar amounts. The activity was present, though in diminished quantity, in acetone powder and was destroyed completely by boiling. The pH optimum was 7.0. The amount of enzyme in ciliary processes compares favorably with the most active tissue investigated previously by Kutscher and Sarreither (1948)—namely, skeletal muscle. The authors suggested three possible functions for the enzyme in ciliary process. They suggested that there may be some need to regulate the level of AMP whether because of its intrinsic nature or because its vasodilator activity might affect the blood supply of the region. Another possibility is that this is an indirect method for regulating physiological processes in which AMP plays an essential part, such as activation of isocitric dehydrogenase, protection of TPN, or involvement in an ion pump.

A curious report by Sowden and Pirie[34] discloses that the choroid of herbivores contains unusually high concentrations of barium. These workers ashed the pooled tissues from several eyes of calf, beef, rabbit, and man and used the rather new technique of activation analysis. By bombardment of the ash with thermal neutrons radioactivity could be induced in the elements of the ash, notably barium and strontium. In each of these, the stable isotope in greatest abundance, barium^{138} and strontium^{88}, absorbs a neutron to form a β-emitting isotope of the next higher atomic weight. By chemical separation with carriers and by radioactivity characteristics, barium and strontium can be analyzed for separately. Curiously, in the calf, the beef, and the adult rabbit eye elevated figures for barium were found, but in the human eye, either newborn or adult, the value was comparable to that found in soft tissue elsewhere. In the cattle only, the sclera was also found to have elevated values for barium but not of the order of magnitude found for the choroid and tapetum. A note on the iris appeared in the papers of Steinvorth and Münich cited above.[1,2] These authors found that glycoprotein analysis of iris and lipoprotein analysis of iris each gave three distinguishable peaks, although further identification of these substances was not made.

The Lens

The literature on the lens during the report period was again plentiful, with interest focused as in previous years on some aspect of the cataract problem. A number of papers dealt with the chemical composition of the lens, and, of these, two concerned the water content. Cascio and Ponte[35] followed the water uptake of calf lenses at 37 C for six hours, with use of assorted media: Tyrode's, aqueous, and blood serum. They weighed lenses each hour and reported the average weight increase for 12 lenses in each group. Over the six-hour period the lenses gained 2%

in weight in serum and nearly 3% for the other two media. In isotonic saline, there was a gain of 17%, indicating more extensive membrane damage from the simpler media. Of all media tried, Tyrode's containing potassium gave the least increase in weight, namely, 1.5% in six hours.

A somewhat more complex set of experiments was performed by Huggert and Odeblad,[36] who investigated the exchangeable water of the cattle lens. Their method involved allowing the lenses to equilibrate with the lens culture medium of Merriam and Kinsey (1950), containing D_2O. At the end of the experimental period, the lenses were removed, rolled in filter paper to remove excess medium, divided into cortex and nucleus, and each sample wrapped in aluminum foil. The D_2O content of each sample was then determined by the ingenious method of Odeblad (1956). In this method the test tube containing the sample is immersed in a flask of $Na^{24}Cl$. Around the flask thin sheets of indium metal are placed and around this paraffin and a lead box. The γ-radiation from the radioactive sodium induces disintegration of the deuterium, each atom of which gives rise to a neutron and a proton. The neutron is absorbed by the indium foil, creating a short-lived radioactive isotope of indium, In^{116}, which emits high energy β- and γ-radiation. The radioactivity of the indium isotope can be measured in a scintillation counter, and when conditions are kept constant there is a nearly linear relationship between indium activity and D_2O content of the original sample. With this technique, one has the advantage of stability and ease of handling of a heavy isotope and the sensitivity of the radioactivity determination.

The authors found that for the cattle and calf lenses used, the final values corresponded to 80% to 90% of the total water content being exchangeable, but the rates of this exchange varied considerably. The exchange for lens nucleus is complete in 10 to 15 hours for older lenses, in 6 to 10 hours for 1- to 4-year-old lenses, and 5 to 6 hours for the lenses of calves. For the cortex, exchange required only one to two hours.

A very careful piece of investigation was reported by van Heyningen and Pirie on acid-soluble organic phosphate compounds in the lens.[37] The work described a chromatographic separation procedure, designed to clarify the discrepancy between the result obtained by an enzymic method and a barium-solubility method in a previous investigation. Most of this work was done on a trichloroacetic acid filtrate of lens, which was divided into a barium-soluble and a barium-insoluble fraction. The barium-soluble fraction was passed through a column of Amberlite IR-120 and then through a column of Amberlite IR-4B. The effluent from the second column was considered the basic fraction, the eluate from the IR-4B column was considered the acidic fraction, and the barium precipitate after decomposition by shaking with Amberlite IR-120 was labeled the barium-insoluble fraction. Precipitation by boiling with dilute acetic acid or extraction of the lens with 80% ethanol at room temperature were used less frequently to prepare starting solutions.

Each of the fractions described previously was chromatographed on paper, and each of the significant substances was demonstrated on the paper by a specific chemical reagent. From the basic fraction, the authors identified phosphorylethanolamine (PE), taurine, glycerylphosphorylethanolamine (GPE), phosphorylcholine (PC), glycerylphosphorylcholine (GPC). The acidic fraction yielded α-glycerophosphate and nucleotides, of which adenosine monophosphate (AMP) and uridine monophosphate (UMP) were positively identified. The barium-insoluble fraction yielded adenosine triphosphate (ATP), adenosine diphosphate (ADP), uridine triphosphate (UTP), and uridine diphosphate (UDP). Of the above, PC, GPC, PE, and GPE had not previously been found in lens. Less positive

identification was made of UMP, UDP, and UTP.

Two very similar reports, also on acid-soluble small molecules, appeared from two other laboratories during the same period. Mandell and Klethi and Duda and Pogell both reported on the acid-soluble nucleotides of bovine lens, and both reports were based on Dowex chromatography of perchloric-acid-extracted lenses.[38,39] Mandell and Klethi separated their lens into three fractions: the capsule-epithelium and thin subepithelial layer, the cortex, and the nucleus. They published values for each of these zones and a calculated corrected value for the epithelium minus the estimated amount of cortex which was adherent to this fraction. The AMP and ADP and the monophosphates of guanosine, uridine, and inosine all were found to be higher in the nuclear portion than in the other zones. However, correction for content of cortex made the calculated value for epithelium alone higher than these. All the other nucleotides found which were di and triphosphates were in higher concentration in the outer zone. These were UDP, acetyl glucosamine (AG), uridine diphosphate glucose (UDPG), cytidine triphosphate (CTP), ATP, and the monophosphates of guanosine (GMP) and uridine.

The identical series with the exception of CTP and with the addition of diphosphopyridine nucleotide (DPN) were reported by Duda and Pogell. These authors also reported the nucleotide contents of corneal epithelium. (Stroma had a small content that was not worked up.) They found DPN, AMP, GMP, UMP, IMP, ADP, UDPAG, and ATP. The content of IMP in corneal epithelium was particularly high.

In the same general area was the determination of the coenzyme A content of animal and human eyes by Pütter and Dardenne.[40] These authors used a water extract of lens deproteinized by isoelectric precipitation at pH 5.85. The supernatant was used in the determination, according to Kaplan and Lipmann, involving the acetylation of sulfanilamide. Their mean figures in micrograms of Co-A per gram of wet weight lens were 16.5 for beef eye, 19.5 for pig eye, and 25.9 for human eye. There was a measurable decrease in the human lens content with age and a sharp decrease in cataractous lenses. The value for man was measurably higher than that for animals.

This report period also saw continuation of the work of Waley on his new tripeptide, which he had named ophthalmic acid.[41,42] In Paper 3 of his series, Waley describes the proof of structure of the peptide which had been isolated earlier and which had been shown to contain glutamic acid, α-aminobutyric acid, and glycine. Paper electrophoresis showed the mobility expected for a γ-linked peptide of glutamic acid. Therefore, the author proposed a structure of glutamyl-aminobutyryl-glycine in exact analogy to glutathione. This structure was proved by synthesis. Benzyloxycarbonyl-1-α-amino-*n*-butyrylglycine was prepared by the mixed anhydrides method. This intermediate was hydrolyzed and reduced to 1-α-amino-*n*-butyrylglycine. The hydrazide of benzyloxycarbonyl γ-1-glutamic acid was converted to the azide and condensed with the above dipeptide, giving a crude product. From this the γ-compound can be obtained by extraction from organic solvent solution with aqueous alkali, followed by precipitation of copper salt and crystallization. This synthetic product proved to be identical in all respects with the naturally obtained material. The author discussed the similarity of this compound to glutathione (GSH) and suggested the possibility that it may act as an anticoenzyme in reactions where GSH is catalytic.

In Paper 4 of the series, Cliffe and Waley[42] describe the biosynthesis of ophthalmic acid. With use of available knowledge about the synthesis of glutathione, the authors were able to devise a system which synthesized ophthalmic acid. The amino

acids or peptides were present in 8mM. concentration except *d*-1-α-aminobutyric acid, which was 16 mM. The mixture contained ATP 2.5 mM., 3-phosphoglyceric 22 mM., KCl 42 mM., $MgSO_4$ 0.4 mM., and phosphate buffer at pH 6.4. Of the 10 ml. of solution, three-fourths represented a one-to-one homogenate of calf lens. The reaction was allowed to proceed at 37 C for five hours. Samples were removed, deprotenized with hot ethanol, and evaporated; the residues were subjected to paper electrophoresis in 10% propanol-2; the product was identified as ophthalmic acid by its chromatographic and electrophoretic mobility, by isolation on paper, by hydrolysis and identification of the amino acids in the proper ratio, and by comparison of an x-ray powder photograph of the copper salt with an authentic specimen.

The yield was affected by the presence of the enzyme γ-glutamyl lactamase which was present in the lens extract and which cyclizes γ-glutamyl peptides to 5-oxopyrollidine-2-carboxylic acid and liberates the second amino acid in the free form. Thus, lens extracts converted γ-glutamyl aminobutyric acid to 5-oxopyrollidine-2-carboxylic acid plus aminobutyric acid. Free glutamic acid and the tripeptide ophthalmic acid did not undergo this reaction.

The authors then outlined the steps in the synthesis as involving two main stages. In the first, glutamic acid plus aminobutyric gave γ-glutamyl α-aminobutyric acid. In the second step, this dipeptide plus glycine gave ophthalmic acid. The presence of the lactamase in lens results in the dipeptide decomposing more than the tripeptide is formed, but still enough tripeptide is available for detection. In the course of isolation of the ophthalmic acid, the authors also found two additional tripeptides: glutamyl-alanylglycine and, probably, glutamyl-threonyl-glycine. These were in much smaller quantity, however, than the butyryl compound.

A number of publications were concerned with the chemistry of the lens proteins. One of these, by Kinoshita and Merola, described the distribution of sulfhydryl groups in glutathione and protein of the lens.[43] These workers determined total SH groups by an amperometric titration, with use of a mercury-mercuric-oxide-saturated barium hydroxide electrode as reference electrode, according to the method of Benesch (1955). GSH was determined by the usual nitroprusside reaction on a trichloroacetic acid filtrate of lens. In one set of experiments, cortex and nucleus were determined separately. In another set of experiments, the α-, β-, and γ-fractions of the lens protein were separated and determined separately. Figures are published both for beef eyes and for calf eyes. The authors found higher glutathione in cortex, higher protein sulfhydryl in the nucleus. In the isolated proteins the β- and γ-proteins are sulfhydryl rich; the α-proteins have a low sulfhydryl content. Young lenses have a greater proportion of β- and γ-proteins and consequently a greater sulfhydryl content than in the adult animals.

A similar report is that of Thomann, who described amperometric determinations of sulfhydryl groups in animal lenses.[44] This author did an amperometric titration of sulfhydryl groups with ammoniacal silver, using a homogenate of lens in distilled water. The apparatus employed a moving platinum electrode versus a mercury-mercuric iodide electrode connected with a salt bridge. The graph obtained shows two slopes whose intersection is the end-point. Nonprotein sulfhydryl was determined on a trichloroacetic acid filtrate from the lens homogenate. The results obtained for beef, calf, and pig lenses which ranged from 406 to 442 mg/100 gm. of lens represent values some 50% of those reported by the American authors.

A Russian communication by Firfarova gives the amino acid composition and the terminal amino acids of α-crystallin.[45] This author described a crystalline preparation of beef α-crystallin, reported by him in 1954, which was homogeneous by electro-

phoresis and ultracentrifugation. It had a molecular weight of 800,000. The protein was hydrolyzed in a sealed vial with 6 N HCl for 24 hours. The dinitrophenyl compounds were made with dinitrofluorobenzene, and these were extracted with ether. The ether extract was evaporated and the residue applied to paper for chromatography. A two-dimensional chromatogram with butanol-ammonia and phosphate buffer at pH 6 develops characteristic spots. Tyrosine and tryptophane were determined spectrophotometrically in the original hydrolysates. The percentage composition was given, and, as might be expected, these differ widely from the figures of Jess (1920).

In more general terms, Hockwin, Newmann, and Kliefeld described the change with age in the three electrophoretically distinguishable proteins of guinea pig and calf lens.[46] They demonstrated that total protein goes up in the beef lens as the lens increases in weight from 1 to 3 gm. The albuminoid rises slowly to 2 gm. lens weight, then rapidly. The crystallins rise to 2 gm. lens weight, then fall. No parallels are drawn with the behavior of α- and β-crystallin, but each of the three electrophoretically separate fractions show distinct differences in behavior.

François and Rabaey[47] investigated the permeability of the capsule for the lens proteins. They used the isolated ox anterior lens capsule as a dialysis membrane. They washed the capsule thoroughly with distilled water to remove all remnants of cells. A container with its open end closed by the lens capsule membrane was filled with distilled water and placed in an extract of ox lens protein at 4 C for 15 hours. After the elapsed time the original extract and the contents of the small container were subjected to microelectrophoresis on agar at about 3 C in barbital (Veronal) buffer. In the extract there was no trace of α-crystallin and no trace of the rapidly migrating fractions. The capsule was highly permeable for the slow fractions designated T-1 and T-2. These are embryonal protein and have low molecular weights. The membrane was also permeable to the most basic of the medium rate fractions, M_4. It is perhaps worth mentioning in this connection that one must be cautious about conclusions drawn from experiments with isolated lens capsule. It was found in my laboratory that any attempt to isolate the lens capsule resulted in complete destruction of the transcapsular potential and with this a presumably drastic change in capsular permeability.[48]

In the papers of Steinvorth and Münich previously cited,[1,2] glycoproteins and lipoproteins of the lens were also investigated, and within each of these categories three peaks were obtained, although the nature of each of these substances was not further investigated.

A report by Halbert and Fitzgerald describes the immunologic organ specificity of the proteins of the lens.[49] These workers immunized rabbits against lens homogenates in Freund's adjuvant, and they used human, frog, teleost (Menhaden), and squid lenses. With use of a modification of the Ouchterlony agar diffusion plate technique, they were able to demonstrate how many bands of precipitate the antiserum against a specific type of lens was able to produce with homogenates of that specific type and the others mentioned. When human lens homogenate was used as the original antigen, seven bands occurred against human lens extract, five of these bands cross reacted with rabbit lens, three with frog, two with the fish, and none with the squid. Against frog antiserum there were five components with frog lens, four with rabbit lens, three with human lens and fish lens, and none with squid, again. Against fish lens four components were demonstrable, three cross reacted with the frog, two or three with human, and none with the squid. The squid lens reacted only with itself, giving four components, one of which was predominant. Additional cross absorption experiments were performed where one antiserum was absorbed with the homogenate and the

remaining components allowed to react with the antigen in the center well. That the number of immunological substances, demonstrated by this method, exceeds the number of proteins generally believed to exist in lens is of considerable significance.

The paper of Dark, cited previously,[8] also contains a description of the lipid in the bovine lens. Using the Sudan black-B stain, Dark described lipid corpuscles in the lens and, particularly, lipid deposits in the anterior lens epithelium.

The metabolic aspects of the lens received less attention during the period in question. However, a study of the C^{14} glucose metabolism of the lens, by Kinoshita and Wachtl,[60] represented a careful repetition of the earlier work done by Kinoshita, in 1955, on the relative amount of glucose metabolism by each of the three major known pathways. In this paper rabbit lenses, cultured according to the technique of Merriam and Kinsey (1950), were utilized as the metabolizing tissue rather than lens homogenates as in the previous paper. A total of eight lenses was cultured for a period of 24 hours in an atmosphere of 7% oxygen, 5% CO_2, and 88% nitrogen. Four of these lenses were given glucose with the C-1 labeled and four with the C-6 labeled. The mean utilization of 27μM. of glucose with production of 41μM. of lactic acid (determined chemically) indicated that glycolysis was the chief pathway. As additional proof, a single lens with uniformly labeled glucose converted 82% of the carbon to lactic acid; there was only 2.3% as CO_2 in this particular experiment, leaving 10% to 17% of the carbon unaccounted for. Comparing the amount of CO_2 produced from C-1-labeled and C-6-labeled glucose, it was found the ratio of C-1 to C-6 was between 33 to 1 and 64 to 1, in comparison with 35 to 50 in the previous work on homogenates—a reasonably close agreement.

The authors concluded that most of the metabolic activity is glycolytic and only 9% to 14% is oxidation. Of this oxidation by far the most is via the gluconic acid pathway. There is little doubt that the major role which the authors assign to glycolysis is correct; there is still some question as to how accurate the ratio between the gluconic acid shunt-pathway and the tricarboxylic acid pathway may be. As was pointed out in connection with the earlier report, if the carbon from the 6-labeled glucose enters a larger set of pools of intermediates in the tricarboxylic acid path than does the 1-labeled glucose in the gluconic acid path, then an erroneous impression of lesser activity by way of the tricarboxylic acid cycle may result from this differential dilution. That both pathways exist and that each is negligible in comparison to the glycolytic path is, however, beyond question.

In the paper by Kuhlman and Resnick, cited previously,[13] the lens of the developing rat eye was studied as well as the cornea. Microsamples of frozen dried lens were dissected out and used for enzyme assay, according to Lowry. The authors suggested that the concentration or the activity of glucose-6-dehydrogenase be considered a measure of the oxidative pathway and the amount of aldolase, a measure of the glycolytic pathway. In both the cortex and the nucleus of the lens, the relative amount of glucose-6-dehydrogenase and presumably the relative importance of the gluconic acid pathway decreases through the course of development. In the capsule plus epithelium there is no change in this activity from the 20th day to adulthood. In lens, too, isocitric dehydrogenase is greater in concentration than glucose-6-dehydrogenase. The authors took this as an indication that the citric acid cycle is possibly of greater importance than credited by Kinoshita (see above). The concentrations of hexokinase, aldolase, and glutamic dehydrogenase are so low that it is difficult to follow the connection between enzyme level and stage of growth. The authors suggested that this confirms the statement of Green that hexokinase is the

limiting step in lens metabolism and that aldolase may be a similar narrow pathway. For the lens, these levels check with the published figure of glucose consumption at 0.14 mg. of glucose per milligram of lens per hour.

A note by De Conciliis and Testa stated that thiaminase is not present in the lens.[51]

Two papers appeared, during 1958, dealing chiefly with a medium for in vitro culture of lenses. From the Kresge Eye Institute (KEI), Wachtl and Kinsey[52] reported a second KEI medium for culture of whole lenses. It differs from their first medium in that α-ketoglutarate was replaced by glutamine; TPN was added, and six of the nucleosides and copper sulfate were omitted. This medium supports the normal level of mitotic activity for 9 hours; the period can be extended to 18 hours without adverse effect on mitotic activity, if the medium is drained and replaced after the 9-hour period. At the end of 24 hours, mitoses have declined to 60% of the normal figure. Glucose consumption and lactate production, however, remain normal for at least seven days, as does the maintenance of ascorbic acid concentration. The concentration of glutathione is maintained for two days.

A similar report is that of Constant,[53] whose medium is based on a standard commercial tissue-culture medium—Difco No. TC-199. In addition to the usual inorganic ions, this medium contains large numbers of amino acids and a number of coenzymes. The chief difficulty was found to be the low buffering capacity of the medium, and when this was increased by adding 9% to 34% of tris buffer (tris [hydroxymethyl] aminomethane), the normal mitotic activity could be maintained for 16 hours. In several experiments with 29% buffer, the activity was maintained for 20 to 24 hours.

Of the papers on the biochemistry of cataract, one by Hockwin and Bergeder[54] dealt with the action of high levels of x-ray on the oxygen uptake of explanted rabbit lenses. The determination was done polarographically and was begun one hour before irradiation. Then 90,000 r were delivered and measurements continued for another hour. Considered over-all, there is a wide scatter and no correlation between the figure for before and after irradiation. If one subdivides the lenses by age, one finds an increase from normal in the average per cent uptake in the embryonal lenses, a decrease in the young lenses, and no effect in middle-aged and old animals. One would be tempted to class short-term oxygen uptake measurements as another one of that large category of determinations which seemed likely to be a measure of lenticular damage but turn out not to be so.

A note by Straub and Krause gives specific details on the protection by cysteine against irradiation cataract.[55] An ample cataractogenic dose is 1,000 to 2,000 r. If cysteine is given subcutaneously in 10% solution at a level of 0.5 gm. per kilogram two hours or less before irradiation, cataract development is prevented.

The article of Seedorf[56] on galactose cataract is significant for its excellent review of the biochemistry of galactosemia to date. Using two cases of galactosemia with cataract in two brothers as his point of departure, Seedorf went on to give an up-to-date picture of the biochemical defect in this congenital disease. He pointed out that in the normal person galactose is utilized by conversion to glucose and is then metabolized along the usual lines that glucose follows. Citing Kalckar and Maxwell,[57] he gives the three steps in conversion of galactose to glucose:

1. Galactose (Gal) + ATP $\xrightarrow{\text{Galactokinase}}$ Gal-1-P
2. Gal-1-P + UDPG $\xrightarrow{\text{Gal-1-P-uridyl transferase}}$ G-1-P + UDPGal
3. UDPGal $\xleftrightarrow{\text{UDPGal-4 epimerase}}$ UDPG

UDPG = uridine diphosphoglucose
UDPGal = uridine diphosphogalactose

The question arises where in the system is the location of the metabolic block, or, to be more specific, the congenital absence of an essential enzyme. In galactosemia there has been demonstrated an accumu-

lation of galactose-1-phosphate, so the block must lie at Step 2 or Step 3. Kalckar was able to demonstrate that in hemolysates or liver biopsy specimens from galactosemics that galactose-1-phosphate uridyl transferase, the enzyme of Step 2, was either very low or zero in concentration; hence, the accumulation of galactose-1-phosphate. Exactly how excess of this compound inhibits the metabolism of glucose is another chapter which is yet unclear.

Finally, one must not fail to mention the year's outstanding example of the application of laboratory biochemistry to clinical ophthalmology. This is the introduction of enzymatic zonulolysis by Barraquer.[58] It was demonstrated by this author that α-chymotrypsin in proper concentration, applied intraocularly for a specific period of time, would dissolve the zonule and not affect other intraocular structures. The result is a lens which luxates with extreme ease, facilitating intracapsular extraction. A procedure for use of a 1:5,000 solution of enzyme is given. Numerous reports have appeared confirming this publication, and the technique promises to be a standard addition to surgical treatment of cataract.

The Vitreous

A publication related to the chemistry of the vitreous is that of Balazs on the physical chemistry of hyaluronic acid.[59] This review deals with work published on hyaluronic acid with a protein content of up to 5%—a degree of purity which is still compatible with a relatively high degree of polymerization. These preparations fulfill the criterion that the hexosamine-hexuronic acid molar ratio is close to 1 and that the nitrogen content is not much higher than would be expected from the hexosamine content. The author pointed out that the hyaluronic acid prepared from bovine vitreous is the lowest polymer of all of the preparations, and he gives an average molecular weight of less than 1×10^6 for it. Balazs describes the various methods of preparing protein-free hyaluronic acid, including electrodeposition, hydrolytic enzyme treatment, and the various attempts to remove the last traces of protein by Celite treatment and use of protein precipitants. In hyaluronic acid preparations from sources other than bovine vitreous, there was little variation in molecular weight by the sedimentation and diffusion methods. Results ranged from 1.44 to 2.0×10^6. The greater variation in results obtained by light scattering may well be due to a difference in polydispersity of the molecule.

In calculating molecular dimensions, much depends upon axial ratios assumed, and apparently there is considerable difference in shape between the high and low molecular weight preparations when subjected to shearing stress in a viscosimeter. This explains greater variation in such figures. The length of the hyaluronic acid molecule from vitreous is 1,600 to 3,400 A. From light-scattering figures of 2,400 to 6,400 A were obtained.

A paper of Blumberg and Ogston[60] dealt with the protein complex of hyaluronic acid from nonocular sources and how the "non-Newtonian viscosity" was affected. Hyaluronic acid from ox vitreous showed no non-Newtonian viscosity and could not be considered in this category.

Several publications dealt with the effect on vitreous chemistry of various pathological situations. A report by Forsius[61] concerned paper electrophoresis of the fluid part of the vitreous from 44 human eyes enucleated for a number of eye diseases, including traumatic uveitis, corneal ulcer, and absolute glaucoma. Electrophoresis was done on paper, and after staining with amino black 10B the densities were measured photometrically and planimetered. Figures are reported for α-1-, α-2-, β-, and γ-globulins, and albumin. However, since many of the determinations were done on fluids containing blood and pus, their value in characterizing disease entities is open to some question.

Cristiansson reported on changes in mucopolysaccharides during alloxan diabetes in the rabbit.[62] In animals that survived the alloxan diabetes with the help of minimum insulin for more than several weeks, serum hexosamine was compared with that of a vitreous filtrate. A significant increase in protein-bound carbohydrate of blood, determined as glucosamine, appears two to four weeks after the onset of the disease and increases progressively with or without insulin treatment. At the same time there is significant increase in the glucosamine of the vitreous, and this can be demonstrated by comparison with one eye enucleated at zero time as a control. The increase is in the order of 30%, a change from 26 mg. per gram to 34 mg. per gram. There is a corresponding increase in the viscosity of the vitreous filtrate and a decrease in its volume. Whether hydration changes play any role in the observed results is not stated by the author.

Changes in the hyaluronic acid of the vitreous under other endocrine situations was reported by Larsen.[63] Total hyaluronic acid was determined as total glucosamine, and an enucleated control eye taken before the beginning of the experiment was compared with the eye enucleated after treatment. Cortisone and thyroidectomy plus thyrotropin gave a significant increase of hyaluronic acid. Thyroidectomy alone gave a questionable increase. In none of these cases is a physiological mechanism adduced.

The effect of iron compounds on the rabbit vitreous is reported by Esquire and McEwen.[64] The effect of injected heme, globin, and two preparations of hemoglobin were investigated in the rabbit vitreous. The authors found liquefaction caused by hemoglobin itself and attributed this to metabolic conversion of the iron to a free ion.

The Retina

Of all the aspects of the chemistry of the composition of the retina, the one that has received the most attention by far is the chemistry of rhodopsin. The period of this review saw a number of new and highly interesting publications on the subject. Perhaps the greatest single concentration of significant papers with chemical orientation was in the outstanding symposium of the New York Academy of Sciences on photoreception. One paper in this series, that of Crescitelli, reviewed the multiplicity of visual pigments that has been isolated from the various vertebrate species.[65] With careful documentation, the author described how the series of retinene$_1$ pigments found in the animal kingdom have absorption maxima which extend from 478 mμ in deep-sea fish to 524 mμ in geckos. With only a single chromophore, the conclusion is inescapable that this spread of 46 mμ must be attributed to the nature of the protein component of the visual pigment.

Corroborative detail is added by the report of Muntz on the photosensitive pigments of deep-sea fishes.[66] Data on six different species of bathypelagic fish revealed absorption maxima of 477 mμ, 485 mμ, 488 mμ, and 490 mμ. One species —Argyropelicus, the hatchet fish—was investigated extensively, and bleaching spectra and oxime were recorded. The presumptive conclusion was reached that the rhodopsin was a compound of retinene$_1$.

The report of Carlisle and Denton[67] concerned the change in retinal pigments in the fresh-water eel at the time of metamorphosis. A purple-colored retina becomes golden-colored in the adult. The chemical significance of this change is not reported.

A fruitful series of publications from the Harvard Biological Laboratory was initiated by the study of Hubbard and St. George on the rhodopsin system of the squid.[68] The visual pigment of the squid is unique, because its photoproduct is not easily hydrolyzable and exists at ordinary temperatures in equilibrium with its rhodopsin. This photoproduct, which corresponds to the substance called metarhodopsin in vertebrate systems, has two

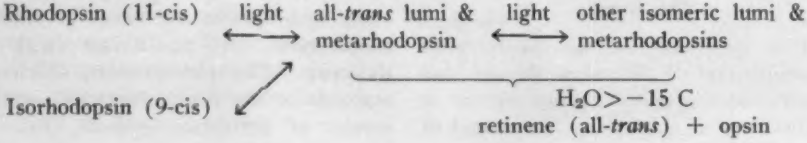
forms, one an acid form with absorption maximum very close to that of rhodopsin at 500 mμ, and an alkaline form which is colorless and has an absorption maximum at 380 mμ. Hence, when squid rhodopsin is acted on by a white light one cannot observe bleaching in acid solution, although in alkaline solution bleaching occurs. By bleaching squid rhodopsin with orange light in alkaline solution, a pure compound can be made which acts as an indicator and for which a titration curve can be plotted as well as a series of spectrograms at intermediate pH values. This series of spectrograms has a single isosbestic point, indicating that only two substances truly exist. The authors found that after this type of irradiation there is no freeing of the aldehyde of retinene for combination with hydroxylamine nor is there freeing of sulfhydryl of protein to parachloromercuribenzoate. Therefore, they conclude that the change in the squid from rhodopsin to metarhodopsin is confined to isomerization of the molecule from the 11-cis form to the all-trans form. They suggested that despite the change in geometric configuration of retinene, the squid opsin is able to accept the all-trans compound as easily as the 11-cis compound. The vertebrate opsin cannot do this: hence, dissociation of the chromophore group occurs spontaneously. It was also concluded that irradiation with white light results in an equilibrium mixture of rhodopsin and metarhodopsin and that light can catalyze the reaction in either direction. This is an aspect of the photochemistry of visual pigments which had not been suspected heretofore.

On the basis of this work, Hubbard and Kropf[69] reviewed the action of light on cattle rhodopsin. They irradiated rhodopsin at −17 C with white light until no further change took place. This gave what was formerly called metarhodopsin. The authors proved that this is an inhomogeneous mixture by bringing it to pH 13 in the dark. At this pH, rhodopsin and isorhodopsin (the 9-cis-compound) bleach slowly, and by decay curves they found that there was in addition a third less stable component. By irradiating at selective wavelengths of 450, 500, and 550 mμ they can favor the formation of this less stable substance. The substance, less stable at the higher temperature, is said to be metarhodopsin. On the basis of this, the authors postulated an equilibrium between rhodopsin, lumi rhodopsin, metarhodopsin, and isorhodopsin all under the influence of light. Above −15 C the metarhodopsin hydrolyzes to all-trans retinene and opsin. This type of system is shown in the diagram on the bottom of the page.

The assumption is made that the actual process of photoactivation, which is the first step in vision, consists in the conversion of rhodopsin to lumi rhodopsin—simply a conversion of the 11-cis configuration to the all-trans configuration—and that the subsequent dissociation is not directly light-dependent.

These findings were reviewed by Kropf and Hubbard in the New York Academy of Sciences Symposium.[70] In this symposium, the authors discussed the theory that rhodopsin is a Schiff base of the aldehyde retinene with a protein amino group. They mentioned that model compounds of this type have absorption maxima at 440 to 450 mμ, well below that observed for rhodopsin. They suggested that interaction between the conjugated bond system of the chromophore and other groups in the protein of the opsin is required to achieve the whole wave-length shift.

In another paper of the same symposium, Oster[71] discussed the same problem of the



discrepancy between the absorption maximum of rhodopsin and that of model Schiff bases with retinene. Oster was unsatisfied with the explanation that this discrepancy can be explained by further conjugation between retinene and protein, for he said that spectral evidence for such resonant structures in the protein does not exist. He said that the absorption spectrum of rhodopsin would be more compatible with the existence of a dimer of the C-20 chromophore, although no chemical evidence for this exists either. On the basis of his experience with thiobenzophenone, he made the suggestion that one may indeed be dealing with a thio-vitamin A aldehyde which is stabilized by its binding to opsin. This would explain the color maximum shift, and conversion of this compound to the ordinary oxygen analog would explain the liberation of sulfhydryl groups with light. However, model compounds have not been able to be prepared as yet, because of the problems of their organic synthesis.

In the same general area is the report of Adams et al.[72] on a system for bleaching rhodopsin at low light fluxes in the presence of hydroxylamine. Under these conditions successive absorption spectra at various times of bleaching show a single isosbestic point and no shift of the absorption maxima. The authors attributed the shift in Wald's early data to reisomerization of all-trans retinene to 11-cis and 9-cis by a second quantum of light (above 69). They postulated that excess hydroxylamine in the surrounding medium is able to combine with the all-trans compound as it leaves the protein and that the oxime so formed will not be isomerized by more light.

An approach to this same problem of the photolysis of rhodopsin from a different direction was described by Wulff and coworkers.[73] A digitonin extract of cattle rod outer segments was irradiated by a brilliant flash from a set of four discharge tubes placed around the rhodopsin cell and delivering a total energy of 64 joules with a half-time of 2μsec. The time course of change of absorption spectrum at each of a series of wave-lengths was followed by means of a separate monochromator photocell system. Analysis of the results indicates three rates of change of density all with different slopes, and the authors suggested that four separate processes are at work, possibly representing transformation of four isomers of retinene, such as published by Hubbard and Kropf.[60] Confirmation of this thesis must await further experimentation, possibly with partial photolysis products of rhodopsin.

A careful investigation of human rhodopsin and its properties was reported by Wald and Brown, who used human eyes from the Boston Eye Bank as a source of material.[74] The preparation was the standard one of separating rod outer segments by differential centrifugation in sucrose, hardening in alum, lyophylization, extraction with petroleum ether, and then solubilization in 2% digitonin solution in phosphate buffer at pH 6.5. This preparation showed a maximum absorption peak at 493 mμ, which the authors considered very short for a vertebrate photopigment. There was a minimum at 390 mμ, a β-band at 350 mμ, and a tall γ or opsin band at 278 mμ. Bleaching in orange nonisomerizing light replaced the α- and β-bands by the absorption characteristic of all-trans retinene with its maximum at 380 mμ. Homogeneity was indicated by a single isosbestic point in the family of absorption curves after successive periods of bleaching up to 35 minutes. The rate corresponded to first-order kinetics. When human opsin is prepared and allowed to incubate with neoretinene *b* (11-cis) from other sources in the dark, rhodopsin indistinguishable from the extracted material, and with a maximum absorption at 493 mμ, can be prepared. Therefore the authors concluded that the position of the peak is a property of the opsin. The kinetics of regeneration follow a second-order reaction with a rate constant, k=0.0084 L. per micromole per minute. This is understandably very slow

in comparison to the rate in situ. In order to try to account for the human psychophysical brightness spectrum with its maximum sensitivity at 500 mμ, the authors measured the absorption maximum of rod outer segments suspended in 40% sucrose to minimize refractive index disparities. They found this preparation to have a maximum absorption of 500 mμ with a narrower α-band. This absorption curve, the scotopic sensitivity curves from five different sources corrected for the absorption of the ocular media, as well as direct measurement of extrafoveal scotopic sensitivity of an aphakic patient all agree precisely.

A similar but smaller shift in absorption maximum toward the long wave-length end was described by Sidman,[75] who worked on frog rods in serum albumin suspension and compared results with those obtained on the rhodopsin extracted from the rods by digitonin.

A paper by Krinsky deals with the lipoprotein nature of rhodopsin.[76] The author identified rhodopsin as an insoluble tissue lipoprotein which can be solubilized by digitonin. The product is a rhodopsin-digitonin micelle consisting of rhodopsin and 180 to 200 digitonin molecules. With use of rhodopsin or opsin extracted from isolated rod outer limbs and dialyzing the extract, Krinsky finds that two-thirds of the phospholipids (which are lecithin, cephalin, and phosphatidyl serine) are bound tightly in the digitonin micelle. Up to two-thirds of the phospholipids can be removed by direct extraction of lyophilized outer limbs with petroleum ether or acetone or ethyl ether at −10 C. If the technique of shaking with ether and freezing at −70 C is used, half of the phospholipids are extractable. If one then bleaches the rhodopsin, more phospholipid is extractable than from the control kept in the dark. This conceivably is connected with other changes wrought by light on the protein, such as the appearance of SH groups. The greatest removal of phospholipid is achieved by treating a sucrose suspension of rod outer segments with phospholipase-C from Clostridium perfringens. There is a rapid decrease in lipid-soluble phosphorus and a simultaneous increase in turbidity due to free diglyceride. With use of this technique, Krinsky estimates a ratio of lipid-soluble phosphorus to rhodopsin of 20, and on this basis he calculates that there are 14,000 gm. of phospholipid per mole of rhodopsin and 18,000 gm. of protein (using 16% nitrogen as the basis for the calculation). Then the molecular weight of rhodopsin equals 32,000, which is lower than the determination of Hubbard. Phospholipase-treated rod outer segments were still able to regenerate rhodopsin to the extent of 85% to 90% after bleaching. It is difficult to say what part the phospholipid plays in the rod physiology. It was suggested by the author that the Schiff's base with retinene may be with an amino group of the phospholipid.

Two papers dealt with the biochemistry of nutritional night blindness. One by Chatzinoff and co-workers describes the injection of vitamin A into newborn rats on an A-deficient diet.[77] When rats were given all-trans vitamin A, 8 units per day were the minimum requirement to prevent generalized systemic symptoms; even here there was some fragmentation of the rod outer segments. When rats were given as little as 2 units per day of the 11-cis isomer, they showed diarrhea and weight loss over the period of the experiment, but the retinas were always entirely normal. Since there were only two to three animals in the experimental group, this work bears repeating, but, assuming its ultimate validity, it connotes some interesting properties of the 11-cis isomer, and it particularly suggests that this isomer is utilized by the eye directly.

In a communication by Dowling and Wald,[78] the authors came to a conclusion diametrically opposed to that of Chatzinoff. This work involved keeping young rats on a vitamin-A-deficient diet but not before

the 22nd to 24th day. It was observed that during the first three weeks of this regime only the liver store of vitamin A decreased. After this time the blood level of vitamin A began to fall, and at four and one-half weeks rhodopsin in the retina decreased; only at the fifth to sixth week did the animal stop gaining weight and the log threshold to the electroretinogram begin to rise. For two weeks thereafter the opsin level remained normal, but by the beginning of the seventh week opsin began to decline and classical symptoms of vitamin A deficiency appeared. No animal survived the end of the eighth week of the experiment. When a severely deficient animal was given a large dose of all-trans vitamin A, the electroretinogram threshold immediately began to fall and reached a normal level in 64 hours. The results on one animal which received the 11-cis isomer showed a lag in recovery in comparison to the all-trans animal, although the threshold reached at 62 hours were identical. On the basis of these two animals, the authors suggested that the 11-cis isomer must be converted to all-trans vitamin A in the body before being able to be utilized by the eye and reconverted to the 11-cis compound. Neither the number of animals used nor the conditions of the experiment make the situation exactly comparable between the two papers quoted. However, because of the considerable theoretical importance of the findings, it might be well worth while to perform a conclusive experiment with larger numbers of animals and resolve this point.

This section could not be considered complete without reference to the superb and esthetically satisfying report of Rushton on the kinetics of cone pigments.[79] By a method similar to that previously published and one which must be read in detail to be properly appreciated, Rushton made measurements in the living human eye—both protanopic and normal—of the change in absorption of the visual pigment of the fovea on bleaching and on regeneration. He presents firm evidence on purely physical grounds that the protanope possesses only one foveal cone pigment and that the normal person possesses two. This series of papers must be considered required reading for anyone interested in the field of visual pigments.

Of the papers on metabolism of the retina, one related also to pigment chemistry, is a report by Krinsky on the enzymatic esterification of vitamin A.[80] This work described how active esterification of vitamin A may be carried on by lypophilized retina, by the pigment epithelium, by rod outer segments, and by the choroid. Control experiments with rat kidney, liver, and small intestine gave no esterification. When the retina is bleached, 60% of the vitamin A present is found esterified. Most of this vitamin A is either in the 11-cis form or the all-trans form. The author suggested that this finding of esterification may indicate the system which isolates the vitamin A metabolism of the eye from that of the rest of the body.

A histochemical study by Nilausen [81] described the location of alkaline phosphatase in the retina of human fetuses of 200 to 600 gm. weight. Freshly fixed tissue was treated by the method of Pearse (1953), and it was found that the entire vascularized area of the retina is phosphatase-positive, with the surrounding avascular zone phosphatase-negative. The enzyme is located only in the nerve-fiber layer, which is where the vessels are at this age. Phosphatase activity was associated with cell formation at the periphery of advancing vessels, with the endothelium of peripheral capillaries, and with individual cells scattered between the vessels.

De Bernardis reported on phosphorylated compounds of the retina separated by chromatography on paper.[82] He did a rather extensive chemical separation before the chromatography, but there was difficulty in identifying any of the spots on the chromatogram with known compounds chromatographed in parallel.

Two papers by Graymore [83,84] dealt with different aspects of retinal metabolism. In the first, Graymore discussed the sharp increase in anerobic glycolysis of the retina which can be demonstrated in the rat during the 10th to 13th day of life. Since this coincides with the opening of the eyes, it is tempting to consider the event as coincident with maturation of the receptor cells. However, if the animals are kept in the dark or if the opening of the eyes is unusually late, the change occurs nevertheless. Graymore's second paper is an investigation of Ashton's suggestion that anoxic swelling might be the basis for vascular obliteration in retrolental fibroplasia. Isolated rat retina was incubated with metabolic inhibitors—iodoacetic acid and sodium fluoride. With each inhibitor the retina was found to increase in weight by 50%.

In a more narrowly defined area, Kinoshita and Masurat investigated the mechanism for formaldehyde oxidation in the retina.[85] These authors were looking for a glutathione-dependent formaldehyde-metabolizing enzyme in the retina similar to that found by Strittmatter and Ball (1955) for liver. They made a beef retina extract by homogenizing, centrifuging, and precipitating the supernatant with 70% ammonium sulfate. This precipitate was redissolved to form the cell-free extract. Rabbit and human retinas were simply homogenized in phosphate buffer and dialyzed. The determination was done by measuring the amount of reduction of DPN in a system containing DPN, enzyme, and GSH. Without substrate there was little reduction. Acetaldehyde goes faster than formaldehyde without glutathione, but glutathione doubles the rate of formaldehyde oxidation in comparison to acetaldehyde. Using lactic dehydrogenase to reduce pyruvate and to reoxidize the DPN, a significant amount of formate could be made and measured. There was nearly a 1:1 ratio of formaldehyde used to formate produced. When glutathione is destroyed by a specific lytic enzyme, no oxidation took place. The optimal amount of glutathione was only 0.5μg. per milliliter of extract, which suggested that glutathione is catalytic in this process. In the human retina oxidation occurred only after a lag period. The pH optimum for cattle extracts is high—in the neighborhood of pH 8. The authors suggested that acidosis may swing the activity away from optimum and let formaldehyde accumulate in the course of methanol poisoning. An additional factor may be the lag demonstrated for human retina and not for animal retina. This, too, might allow formaldehyde accumulation in methanol poisoning and account for the difference between primate and nonprimate poisoning.

Two papers which appeared simultaneously described the identification of a pathological entity whose true chemical nature had escaped detection until now.[86,87] In eye tissues which have undergone long-time degeneration, particularly in the case of retinal detachments, pathologists had noted birefringent crystals which had been named "protein crystals." The simultaneous publications of Cogan and co-workers and of Zimmerman and Johnson identified these crystals as primarily calcium oxalate with admixture of calcium phosphate. A series of independent spot tests made the identification beyond question, and x-ray powder analysis in the case of the Cogan report provided final confirmation.

One additional item on the pathology of the retina worth mentioning is the report of Sorsby and Nakajima on the effect of various metabolic inhibitors in causing retinal degeneration.[88] A series of 14 known inhibitors of metabolism were given in just sublethal dose, but only in the case of a combination of sodium fluoride and sodium cyanide were the authors able to obtain any histological evidence of retinal degeneration. This indicates that the retinotoxic agents which have been found in quantity during recent years must have either a more specific or a more potent effect than simple inhibition of energy-producing mechanisms in the tissue.

Tears

In a third report on the electrophoresis of tears, McEwen, Kimura, and Feeney [89] described the components of normal tear secretion as (*a*) lysozyme, (*b*) three distinct nonalbumin components, and (*c*) at least two albumin components, one designated tear albumin and one which corresponds to serum albumin. Component *bIII* and possibly Component *bII* are mucoprotein, but Component *bI* has not been more positively identified. All three *b* components are resistant to trypsin, to hyaluronidase, and to chitinase. Component *bI* is absent or very low in tears caused by irritating agents or by emotion. The implication of these findings for functioning of the lacrimal gland was discussed by the authors.

A paper by Erickson, Hatten, and Berg [90] described a technique for electrophoresis of tears similar to that already published by McEwen and Kimura (1955). In addition, there are published four sets of results, each from a single person with an eye complaint. The implication is that the specific tear patterns are characteristic of the eye disease. Such conclusions must be based on a much more extensive series.

A report by Rexed [91] described the pH of tears stimulated by filter-paper irritation and collected at the opening of the lacrimal duct in a capillary made of Corning 0.015 glass. The capillary was then used as a glass electrode in a standard manner. In 100 subjects the range of pH was found to be 7.1 to 7.99. The distribution was given as 7.49 ± 0.02, with a standard deviation of 0.16. This figure is useful, of course, for our knowledge of the physiology of the lacrimal gland. Because of the paucity of tears under normal situations, we still have no adequate way of knowing what the ordinary environment of the corneal epithelium may be.

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Correspondence

RADIOACTIVE ISOTOPES

To the Editor:—My attention has been directed to an article by Dr. J. W. Bettman, in A. M. A. ARCHIVES OF OPHTHALMOLOGY (59:821 [June] 1958), entitled Radioactive Isotopes.

I quote from page 825 paragraph 15: "The therapy of intraocular tumors, usually retinoblastomas, by suturing radioisotopes to the sclera,[29,31,34] . . . is not new. . . . They depend upon β-emissions for their therapeutic effect, the α-emissions not penetrating the eye and the γ-emissions being very weak." The three references given here include one to an article by Dr. Arthur Joyce and myself entitled Treatment of Intraocular Tumors with Radon.

This statement concerning radon seeds which we use is not correct.

The radon seeds are prepared by the Commonwealth X-ray and Radium Laboratory and have wall thicknesses of gold equivalent to platinum filtration of either 0.3 or 0.5 mm.

No α-rays are emitted, the β-ray contributions through the above filtrations are approximately 10% and 0.5%, respectively, and the rest of the radiation is γ-radiation. Naturally there is soft secondary irradiation from the surface of the seeds due to absorption of the radiations by the wall filter material. The therapeutic effects obtained from our seed implants are essentially due to the γ-radiation.

Because of the minute size of the 0.3 Pt. equivalent wall gold seeds (total length, 2-3 mm.), the low strength at which they may be used (0.2 mc. and upwards), and the overall small diameter (0.78 mm.), we have preferred these sources for our work with intraocular tumors. We have been able to suture these seeds with great accuracy on any required part of the scleral surface. Suturing is facilitated by a small groove pressed into the body of the seed at the time of preparation.

In using 0.3 Pt. equivalent radon seeds we accept the small proportion of β-radiation, knowing from our experience that such is not harmful if the seeds used are weak.

Dr. Bettman further states on page 822 paragraph 2, "Gamma emissions are the equivalent of x-rays. . . . Because these emissions penetrate through the entire head they are of little use in ophthalmology."

It may be said that the γ-radiations "penetrate the entire head," but this statement is somewhat misleading. With the small quantities of radon used the fall-off of radiation intensity from the sources is so great that the radiation would produce no possible therapeutic or biological effect at distances of more than a centimeter or so. The dose received by tissues like the lens and conjunctiva, which may be within a range of a few millimeters of seeds sutured to the sclera, is of concern to us and is calculated.

However, we have overcome excess dosage effects on the conjunctiva by the use of plastic conformers fixed over the seeds. The conjunctiva is sutured over these conformers so that its distance from the sources is increased and so that the dose received by it is reduced. The danger to the lens is minimized by the arrangement of the seeds according to Paterson and Parker rules and by the lowest reasonable dose prescription, so that the smallest dose possible is received by the lens. These complications are only likely to arise when the tumors are very far forward near the ciliary body.

Radon seeds as used in Australia are made of gold capillary tubing. A long length of capillary is evacuated of air and is filled with purified radon gas. The capillary is cut into short pieces of predetermined length so that each segment or "seed" contains a required amount of radon. The gold tubing is cut with blunt forceps which seal the capillary cavity. Two pure gold surfaces brought together under pressure will fuse by a process of welding even in the cold, and so a hermetic

seal is obtained. The forceps have a micrometer screw device which allows the seeds to be cut with accuracy to lengths varying by 0.1 mm. Seeds of content 0.5 to 1.0 mc are usually individually accurate to within ±5%. Weaker seeds of short lengths—2 to 3 mm. as used in our ophthalmological work—may vary slightly more than this figure, but the Commonwealth X-ray and Radium Laboratory, which prepares the seeds, guarantees that the total content of the batch used is accurate to within ±2%.

We feel it necessary to correct the statement in Dr. Bettman's article as quoted above and to point out that treatment with radon seeds in Australia is essentially γ-ray therapy, which, contrary to his assertion, has an essential but restricted field of usefulness in ophthalmological practice.

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To the Editor:—Thank you for forwarding the comments of Dr. R. Kaye Scott. All of his statements are quite correct.

One of the apparent disagreements arose from a misunderstanding of what my article referred to. I quote from it: "[γ-Emissions] are of little use in ophthalmology. If an isotope emitting γ-radiation is given intravenously and a Geiger-Müller tube is held over the eye, the radioactivity from the entire head 'drowns out' the radioactivity from the eye itself." This refers to the use of these isotopes in detecting tumors in the eye (as diagrammed in the original article) or in the detection of blood volume changes (as in the other diagrams). In either of these situations γ-emissions from the entire head do give rise to so much radioactivity that it is difficult or impossible to detect any changes in radioactivity originating from the eye itself. Thus they do "drown them out." The use of isotopes as a substitute for x-ray therapy, such as the cobalt bomb, was not considered within the scope of the article. The only other situation in which γ-emissions are useful in ophthalmology is in the therapy of certain tumors, such as retinoblastomas. In my opinion this is rarely indicated, as explained below. Therefore, "[γ-emissions] are of little use in ophthalmology."

The other statement of Dr. Scott corrects an error in my article which was meant to be "Regardless of the isotope used, the only effective emanation is the gamma, since the alpha and beta emissions are filtered out by the ½ mm. thick platinum casing. . . . However, if an undiscovered small island of retinoblastoma is present on the opposite side of the eye or a few seedlings are floating in the vitreous, an effective dose of radiation may not be delivered." This quotation is as I stated it in the *Transactions of the Pacific Coast Oto-Ophthalmological Society* (39:261, 1958) and as it should have also been stated in the Archives. It explains why I believe that radon seeds and related types of therapy for retinoblastomas are inferior to x-ray.

I apologize to Dr. Scott for the error and thank him for clarifying it.

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Society Transactions

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Harold G. Scheie, M.D., Chairman
William E. Krewson III, M.D., Clerk

Jan. 15, 1959

A Case of 'Total' Choroidal Detachment Following Cataract Surgery. Dr. H. Walter Forster Jr.

A 79-year-old male diabetic had an uncomplicated intracapsular cataract extraction. The chamber was reformed with air at the end of the operation and was never shallow or flat. Choroidal detachment did not develop until after discharge from the hospital and was first discovered on the 15th postoperative day. The anterior chamber was always deep. The choroidal detachment, however, progressed until the 20th postoperative day, at which time the nasal and temporal segments of the detachment came in contact with each other and all light perception was lost. At this point a scleral trephination in both lower quadrants was done, releasing large quantities of subscleral fluid, and air was injected into the anterior chamber forcing the vitreous back. Light perception returned on the following day. The end-result was recovery of vision to 6/12 with aphakic correction. It would have been better except for diabetic retinopathy.

The discussion following the case presentation concerned the mechanism of choroidal detachment. There was no unanimity of opinion regarding the necessity for the presence of a wound leak. The case, in which the detachment occurred late, did not have one. There are a number of unanswered questions regarding the fate of the vitreous in an eye with extensive choroidal detachment. No one else present reported having seen a choroidal detachment in which light perception was lost.

Repair of Orbital Deformity with Plastic Sponge Implant. Dr. Robert D. Mulberger (by invitation) and Dr. G. M. Shannon (by invitation).

The authors briefly reviewed the literature on the use of polyvinyl plastic sponge material for tissue implantation.

A movie and description of the operative technique employed was presented. The authors believe that this is the first report of the material being employed to build up the orbital floor, although they realize that it has been used before by several others for this same purpose.

The authors conclude that their experience with polyvinyl plastic sponge to raise the orbital floor in orbital deformity has been satisfactory.

Feb. 19, 1959

Surgical Treatment of Blepharoptosis. Dr. Raynold N. Berke (by invitation).

The final result of ptosis surgery depends on three factors: the skill of the surgeon, the nature of the ptosis, and the type of operation done.

However skilled the surgeon may be, it is still impossible to achieve a perfect cosmetic and functional result in all types of ptosis by any procedure available to us today. This is so for two reasons. First and most important is the complex nature of some types of ptosis, such as ptosis complicated by severe blepharophimosis, ptosis associated with the jaw-winking phenomenon of Marcus-Gunn, and ptosis due to complete third nerve paralysis. Second is the observation that all ptosis operations carry some inherent disadvantages which of themselves prevent a perfect result.

Frontalis Ptosis Operation: If one is successful in fully correcting the ptosis in the primary position by suspending the lid from the brow, then after operation there is always lagophthalmos in looking down and ptosis in looking up unless the brow is elevated to raise the lid. For these reasons the frontalis type of operation is not the procedure of choice for all patients with ptosis, especially when the ptosis is monocular.

However, when the ptosis is binocular and fully corrected in the primary position these objections are much less serious be-

cause the ptosis in upward gaze and the lagophthalmos in looking down is equal on the two sides.

Therefore, it would seem that the frontalis operation is the operation of choice for binocular ptosis when resection of the levator is contraindicated and for monocular ptosis only when the levator and the superior rectus muscles are too weak to support the lid.

Superior Rectus Ptosis Operation: The main advantages of suspending the lid from the superior rectus muscle are that the lid moves synchronously with the globe in upward and downward gaze, a good upper lid fold is produced, and a natural curve of the upper lid margin results when wide adhesions are produced between the tarsus and the superior rectus muscle.

The disadvantages are that some hypotropia is usually present in upward gaze after operation, even though the superior rectus is shortened at the time of operation; normal winking is destroyed, and there is lagophthalmos in sleep with a tendency for exposure keratitis to develop.

For these reasons this type of operation should not be used for all types of ptosis. Despite these objections, however, it is the operation of choice for jaw-winking ptosis when the superior rectus muscle is normal or near normal, provided the superior rectus is shortened to enhance its lifting power and a large part of the levator is excised to eliminate the jaw-winking phenomenon.

Resection of the Levator Muscle: Because resection of the levator is the only operation which can give a perfect result, most seasoned ophthalmologists believe that it is the operation of choice for all types of ptosis (except jaw-winking ptosis) when the levator action is adequate. However, there is an honest difference of opinion as to which operation—the internal or the external approach—gives the best results.

In order to resolve this question, I have analyzed the results of 186 operations done for congenital ptosis—78 of which were done through the conjunctival approach and 108 through the skin route. Because the cases were all congenital and not selected in each group, because the operations were all done at the same institution by essentially the same resident and attending surgeons, and because all the preoperative and postoperative examinations as well as the details of the operation were all collected and analyzed by the same person, this appraisal of the relative merits of the two procedures should be a fair and valid one.

This survey showed that the external approach produced 1 mm. more correction and about 20% fewer undercorrections than did the internal route.

When overcorrection followed the skin approach it was usually associated with good levator action (8 mm. or more) and a postoperative "lift" of the operated lid with respect to the cornea—that is to say, the lid assumed a higher position on the cornea when healing was complete than at the end of the operation.

Undercorrection usually occurred when the levator action was poor (5 mm. or less) and was associated with a postoperative "fall" of the lid, i. e., the lid covered the cornea more when healing was complete than at the end of operation. When the levator action measured 6-8 mm. in amount before operation the operated-on lid usually assumed the same position on the cornea as at the end of operation.

From this survey it would seem that (1) the frontalis type of ptosis operation is the procedure of choice for complete bilateral ptosis with little or no levator action and for those cases of monocular ptosis where the levator and the superior rectus muscles are too weak to support the lid; (2) the superior rectus muscle should be utilized to correct the ptosis when associated with the jaw-winking phenomenon, provided the superior rectus is shortened to enhance its lifting power and a large part of the levator is excised to cure the jaw-winking; (3) resection of the levator through the skin route is the operation of choice for congenital ptosis when some levator action is present, taking care to overcorrect the ptosis on the operating table when the levator action is poor and to undercorrect it when the levator action is good.

March 19, 1959

Angiomatosis Retinae: A Report of Two Cases Operated On. DR. DAVID SEAMAN (by invitation).

Angiomatosis retinae is characterized by a pair of grossly enlarged blood vessels which course from the disc to the retinal periphery and terminate in an elevated circumscribed tumor. Throughout the retina are scattered collections of lipoidal vascular exudates.

One hundred seventy-five cases have been reported in the literature.

Two patients, aged 4 and 20 years, recently operated on at Temple University

Medical Center were reported. In both cases the angiomata were uniocular. In neither case was there any evidence of central nervous system or general systemic involvement.

In each case the sclera was exposed over the tumor site and penetrating micropins were placed into the tumor. Several applications of diathermy coagulation were employed with use of a current of 40 ma for eight seconds per application over the tumor area. No intraocular hemorrhage occurred.

The appearance of the tumor did not change immediately after diathermy, but subsequently the angiomata became much smaller in circumference and showed a 50% decrease in elevation. A follow-up study is planned to determine the necessity of further therapy and to watch for development of additional angiomata.

Management of the Patient with Sub-Normal Vision. DR. BERNARD C. GETTES.

In December, 1955, a Low Vision Clinic was established at the Wills Hospital. Approximately 300 (285) patients have been seen in consultation since that time. The following data is submitted on the basis of these examinations.

1. One can prognosticate which patients are suitable candidates for a visual aid. This is based on the following:
   (*a*) Proper motivation
   (*b*) Visual acuity of at least 20/500
   (*c*) An adequate peripheral field
2. Selection of the applicant is based on the patient's visual acuity which was tested in many ways, as follows:
   (*a*) Stimson Target Test Charts
   (*b*) Keeler Near Charts
   (*c*) Sloane Near Charts
   (*d*) Lebensohn Test Charts

(These charts were evaluated and found to be comparable in their purpose.)

The method of testing is not difficult. The Stimson Charts appear to be the easiest to utilize from the standpoint of the patient and the examiner.

3. Testing and examination of the patients does not require a special clinic, nor does it necessitate expensive equipment.
4. Statistical data is submitted to show how many patients have been benefited.

Corticotropin and Corticosteroids in the Treatment of Herpes Zoster Ophthalmicus. DR. HAROLD G. SCHEIE and DR. THOMAS G. MCLELLAN JR. (by invitation).

The report summarizes results of treatment of 25 cases of herpes zoster ophthalmicus, all with intraocular involvement. The usual initial dose of corticotropin was 40 units intravenously in an eight-hour infusion. When progressive improvement had occurred, intramuscular therapy was substituted; a few days before parenteral therapy was stopped, oral corticosteroids were started in standard doses. Pain was usually relieved within 48 hours of starting therapy. Ciliary flush decreased after the first day of therapy. Clearing of the aqueous was noted. Clearing of the aqueous began in 48 to 96 hours. Six patients had recurrent iridocyclitis after the initial attack had subsided and all medications had been stopped. Recurrences were readily controlled by resuming oral corticosteroid therapy.

In a total series of 36 patients so treated 2 have shown significant visual loss. Thirty-four have retained normal vision. The authors believe that at present systemic corticotropin and corticosteroids are the treatment of choice for herpes zoster ophthalmicus.

News and Comment

ANNOUNCEMENTS

Meetings of Association for Research in Ophthalmology, Inc.—The following dates for regional and national meetings of the Association for Research in Ophthalmology, Inc., have been announced. The bylaws of the Association require that all papers presented at the national meetings be published in the supplements. Publication of papers from section meetings is optional.

Midsouthern Section — Nov. 13 and 14, 1959
Jesse Jones Library Building, Texas Medical Center, Houston, Texas
Louis Girard, M.D., Chairman, Hermann Professional Building, Houston, Texas

Southeastern Section — Dec. 3, 4, and 5, 1959
Medical College of Georgia, Augusta, Ga.
John R. Fair, M.D., Chairman, Medical College of Georgia, Augusta, Ga.

Midwinter National Meeting — Dec. 3, 4, and 5, 1959
Medical College of Georgia, Augusta, Ga.
Lorand V. Johnson, M.D., Chairman, 10515 Carnegie Ave., Cleveland 6

East Central Section — Jan. 4, 1960
University of Michigan, Ann Arbor, Mich.
Harold Falls, M.D., Chairman, University Hospital, Ann Arbor, Mich.

Eastern Section — Feb. 18, 1960
Wills Eye Hospital, Philadelphia
Thomas R. Hedges Jr., M.D., Chairman, 1711 Rittenhouse Sq., Philadelphia 3

Midwestern Section — April 23 and 24, 1960
Indiana University Medical Center, Indianapolis
Fred M. Wilson, M.D., Chairman, Indiana University Medical Center, Indianapolis

National Meeting — June 12-17, 1960
Miami, Fla., Lorand V. Johnson, M.D., Chairman, 10515 Carnegie Ave., Cleveland 6 (Abstract deadline—Dec. 15, 1959)

Refresher Course in Eye Surgery at the University of Toronto.—The Department of Ophthalmology, in collaboration with the Division of Postgraduate Medical Education of the Faculty of Medicine, University of Toronto, offers a refresher course in Eye Surgery, April 4-5, 1960.

In addition to the staff of the department, three guest surgeons will take part in the teaching: Dr. Graham Clark, New York; Dr. Robert J. Brockhurst, Boston, and Dr. Saul Sugar, Detroit. Operative clinics will be given in the University Teaching Hospitals each morning; formal clinics, lectures, and case presentations will be given in the afternoons. There will be symposia on glaucoma and retinal detachments.

The course will be given to a minimum of 10 and a maximum of 35.

The fee for the course will be $40, payable to the Chief Accountant of the University of Toronto at the time of application, which should not be later than Feb. 15, 1960. Further information and application forms may be obtained from the Division of Postgraduate Medical Education, Faculty of Medicine, University of Toronto.

Future Meetings of the Association for Research in Ophthalmology, Inc.—Letters of intention to present papers may be *immediately* sent to the chairman of each meeting.

Midsouthern Section: Nov. 13, 14, 1959; Jesse Jones Library Building, Texas Medical Center, Houston, Texas; Louis Girard, M.D., Chairman, Hermann Professional Building, Houston, Texas.

Southeastern Section: Dec. 3-5, 1959; Medical College of Georgia, Augusta, Ga.; John R. Fair, M.D., Chairman, Medical College of Georgia, Augusta, Ga.

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National Meeting: June 12-17, 1960; Miami, Fla.; Lorand V. Johnson, M.D., Chairman, 10515 Carnegie Ave., Cleveland 6; *Abstract Deadline—Dec. 15, 1959.*

SOCIETY NEWS

Officers Elected.—At its recent meeting, the American Ophthalmological Society elected the following officers:

President: Dr. Algernon B. Reese, New York
Vice-president: Dr. Edwin B. Dunphy, Boston
Secretary-Treasurer: Dr. Maynard C. Wheeler, New York
Editor of Transactions: Dr. M. Elliott Randolph, Baltimore

Societé Française D'Ophthalmologie.—The French Society of Ophthalmology held its 66th Congress in Paris, May 10 through 14. This happened to be the 75th Anniversary of the foundation of the Society. The meeting was therefore particularly important. A great number of foreign members had come for this exceptional occasion, and the U. S. A. was represented by Conrad Berens (New York), R. Castroviejo (New York), Mrs. Daily (Houston), and Brittain Payne (New York).

The opening session of the meeting, on Sunday morning, May 10, was devoted to the commemoration of the 75th anniversary with the Secretary of Health in the Chair. The speeches were delivered by Mr. René Onfray, of Paris, who gave a brief account of the French Society since its birth; Mr. Hambresin, of Brussels, who spoke in the name of the European ophthalmologists; Mr. C. Berens, of New York, representing North America; Mr. Hilton Rocha, of Bello Horizonte, Brazil, representing South America; Mr. Misao Uyemura, of Tokyo, representing Asia, and Mr. Mohamed Aouchiche, of Dakar, representing African ophthalmologists.

On Monday morning, May 11, papers were on the ciliary body. Jacques Mawas (Paris) had studied the nerves in the ciliary body where they are particularly abundant; there are also a few ganglion cells. The discussion was opened by Guy Offret (Paris). A. Brini and Porte (Strasbourg) studied the ciliary body through the electron microscope; they found first a row of cells in contact with the aqueous, which were already observed by Pease; below a layer of pigmented cells, and finally the stroma; the discussion was opened by J. François (Ghent). Nico Trantas (Athens) reported some cases of atrophy of the trabeculum; there are some cases where the atrophy is caused by a trauma, but more interesting are those observed in glaucoma, uveitis, and Fuch's syndrome; the discussion was opened by J. François (Ghent), P. M. Amalric and co-workers (Albi) stressed that the pathogeny of Fuch's syndrome was still unknown; experimenting on the sympathetic in the rabbit they were unable to produce it; they think that there must be some link between Fuch's syndrome, simple congenital hetechromia, and the heterochromia secondary to a lesion of the sympathetic. The discussion was opened by Bernard Streiff (Lausanne). Hilton Rocha (Bello Horizonte) ques-

tioned whether there could exist a sympathetic ophthalmitis without any perforation; he reported on a case of serous uveitis and ophthalmomalacia in one eye, followed later by serous uveitis in the other, and where serial sections showed no perforation but typical sympathetic ophthalmitis. The discussion was opened by P. Desvignes (Paris). Emile Zenatti (Paris) considered that tonosphygmography can be useful in the diagnosis of chronic glaucoma; thanks to this method, one can measure the blood pressure in the choroid, and in glaucoma this pressure is always found high; the discussion was opened by Paul Bailliart (Paris). G. Offret, C. Haye, and R. Campinchi (Paris) showed slides of an eye operated on five days previously for cataract under α-chymotrypsin, the patient having died of coronary thrombosis; the corneal wound was healing normally, the hyaloid was normal, and there was no ciliary vasodilation, but there was an exudate on the surface of the ciliary body. The discussion was opened by J. Nordmann (Strasbourg). A. Busacca (Sao Paulo) read a paper on the anatomical and embryological basis of chemical zonuolysis; he stressed that the hyaloid was composed of two parts, one derived from the final vitreous, the other from the hyaloid vitreous; according to him, the α-chymotrypsin disolves both the zonula and the final vitreous but does not touch the hyaloid vitreous. The discussion was opened by G. Lepat (Liège). G. Renard and P. Dhermy (Paris) presented a case of epithelioma of the sinus which had penetrated the orbit and even the eye. The discussion was opened by G. Offret (Paris). Naci Bengisu and Sezer (Istanbul) were able to isolate and cultivate Sezer's virus in the hypopyon of a case of Behçet's disease; the discussion was opened by E. Hartmann (Paris). A Bouzas (Athens) read a paper on three cases of Behçet's disease with neurological symptoms; the discussion was opened by L. Calmettes (Toulouse).

On Monday afternoon, May 11, free papers were presented. E. Laine and P. François (Lille) reported three cases of aneurysm of the internal carotid artery; they stressed the pathogeny and also the difficulty of the diagnosis with a pituitary tumor. The discussion was opened by P. Bonnet (Lyons). P. Wertheimer and co-workers read a paper on Parinaud's syndrome. Out of 2,000 cases of brain tumors, 20 had Parinaud's syndrome; in the majority of cases the tumor could be localized in the thalamic area. The discussion was opened by P. Bregeat (Paris). H. Viallefont and co-workers read a paper on the roentgenological examination of the cavernous sinus after injecting a contrast liquid in the angular vein; the discussion was opened by P. Bregeat (Paris). W. H. Melanowski (Warsaw) in cases of optic nerve tumors advised simple orbitotomy as the best operation; the discussion was opened by A. Vergez (Paris). Jean Mergier (Paris) observed a case of orbital cholesteatoma; the discussion was opened by G. Lombard (Paris). W. Straub (Hamburg) reported on the toxic effect of hydroquinone on the conjunctiva and the cornea; 13 workmen out of 17 handling this substance were affected. The discussion was opened by G. Offret (Paris). J. E. Winkelman and G. P. M. Horsten (Amsterdam) studied the electroretinogram in the newborn; this they found possible, and they compared it with results obtained with the young dog. L. Druault-Toufesco (Tours) found that there was a constant relation between the weight and the diet of a diabetic patient and the condition of his retina. The discussion was opened by F. Deodati (Toulouse). L. Calmettes and co-workers (Toulouse) reported on seven cases of "dysoric" retinitis and considered that this trouble, observed in patients with very poor general condition, was due to a disturbance of the capillary permeability; the discussion was opened by G. Bonamour (Lyons). H. Remky (Munich) read a paper on uveitis in acquired toxoplasmosis (20 cases); the discussion was opened by J. François (Ghent). G. Perdriel and co-workers studied the effect of altitude on contact lenses. They found that at an altitude of over 5,500 meters, air deposited under the lens with resulting corneal lesions and visual impairment; by the use of methyl-cellulose, this trouble was avoided. The discussion was opened by A. Mercier (Tours).

On Tuesday morning, May 12, Jules François (Ghent) presented the main paper of the Congress. This year it was on congenital cataracts. Little by little, the main papers at the French Society of Ophthalmology had become larger and

larger, and for the last 20 years, at least, they are thick volumes of well over 500 pages. François' book has 853 pages and 506 figures, 20 of which are in color.

The first chapters are devoted to the embryology of the lens, the anatomy, and the description of several congenital anomalies of the lens (besides cataract). The following chapters classify the congenital cataracts (capsular and capsulolenticular cataracts, total and regressive cataracts, cataracts developed in a normal or an abnormal fetal lens). A few pages are devoted to early postnatal cataract, anomalies often associated with congenital cataract, and ERG in congenital cataracts. Several general syndromes, of which the congenital cataract is a part, are throughly described. Next come six chapters devoted to the different causes of cataract. Heredity is here well studied. The treatment is then discussed (surgical techniques, time of operations, general anesthesia, postoperative complications, postoperative treatment, and final results). The book, written by François, is a very fine piece of work.

It was distributed free of charge to all members of the French Society, but nonmembers can purchase it by applying to the publisher, Masson & Cie., 120 bd. Saint Germain, Paris 6. The price of the book is 11,000 fr. (about $22). After this presentation, which lasted an hour, a few papers were read on the same subject. P. Valissaropoulos and C. Topalis (Athens) reported on the use of α-chymotrypsin in operations on congenital cataract. The results in the Athens Clinic were very good. The discussion, opened by L. Paufique (Lyon) followed by J. Barraquer (Barcelona), tended to discourage the use of this procedure in patients less than 10 years old. C. Avanza and Balavoine (Geneva) described a new type of cataract (cataracta umbilicata) associated with brachymorphia and external ophthalmophlagia, which was found in three brothers. A. Franceschetti and P. Dieterle (Geneva) discussed the relationship between "Pagoda-like" cataract and central powdery cataract. S. Delthil and M. Crouzet (Paris) read a paper on cataract and congenital malformation in children of amblyopic classes in Paris. These papers were followed by a general discussion.

During the afternoon films were shown.

Wednesday morning, May 13, papers were on neuro-ophthalmology. Petit-Dutaillis and co-workers (Paris) read a paper on cases of pituitary adenomas with abnormal symptoms; the discussion was opened by Bregeat (Paris). Bregeat and co-workers described changes of the visual fields in oculomotor paralysis of long standing; they are similar to those observed in strasbismus amblyopia. The discussion was opened by A. Dubois (Paris). F. Thiebaut and N. Matavulj (Strasbourg) read a paper on visual field anomalies in temporal lesions; the discussion was opened by Louis Guillaumat (Paris). M. A. Dollfus and co-workers (Paris) reported on the disc and the retina in 478 cranial traumas; the discussion was opened by P. Bregeat (Paris). M. Massin (Paris) discussed the decision to be taken when the optic nerve suffers after a cranial trauma; he had observed 66 cases. The discussion was opened by M. A. Dollfus (Paris). P. Desvignes and co-workers (Paris) reported on late impairment of vision after cranial trauma; the discussion was opened by B. Streiff (Lausanne). A Ricci and Maeder (Geneva) reported on two cases of very probable hysteric blindness; the discussion was opened by E. Hartmann (Paris). H. Saraux and F. Martin (Paris) had observed 50 cases on tonic pupils and discussed the relationship with Adie's syndrome; the discussion was opened by P. V. Morax (Paris). M. Ardouin and co-workers (Rennes) had observed 16 cases of multiple sclerosis and believed that there were some fairly typical lesions of the fundus in this disease (arterial changes, thrombosis of some veins, pigment deposits in the choioretina, opacities, and even hemorrhages in the vitreous); the discussion was opened by M. Paufique (Lyon). J. Zanen (Brussels) read a paper on the photochromatic interval in neuro-ophthalmology; the discussion was opened by A. Dubois-Poulsen (Paris). M. Collier (Pau) reported on a case of late epilepsy with dyskeratosis of Darier and hemihypertrophy; the discussion was opened by E. Bessière (Bordeaux).

Thursday morning, May 14, was devoted to three papers. S. Postic (Novi Sad) read a paper on the etiology of chronic follicular conjunctivitis; the discussion was opened by G. Bietti (Rome). I. Vassilev (Sofia) advocated the surgical treatment of xerosis (technique of Fillatow-Schewaljow); the discussion was opened by

L. Paufique (Lyon). E. Rosselet and co-workers (Lausanne) read a paper on tuberculous uveitis in children. They found that these responded well to antibiotics and sanatorial cures; the use of corticosteroids was debatable. The discussion was opened by P. V. Morax (Paris). A. Larmande and J. Orfila (Algiers) discussed the comparative morphology of the Weeks and Pfeiffer bacilli when examined with the electronic microscope; the shapes of the two bacilli were found to be different. The discussion was opened by J. Mawas (Paris). O. Litricin and I. Stankovic (Belgrade) read a paper on the primary malignant tumors of the cornea; the discussion was opened by F. Hervouet (Nantes). Jean-Sédan and co-workers advised a psychomotor study of students intending to specialize in ophthalmology; the discussion was opened by C. Coutela (Paris). L. Valk (Helmond) advised, in diabetic retinophathy, the use of nor-androsténolonphényl-propionate; the discussion was opened by M. A. Dollfus (Paris). A Zuccoli (Lugano) advocated diathermocoagulation through the conjunctiva in the prophylactic treatment of retinal detachment; a temperature of 60-65 C is reached within 5 or 6 seconds and is maintained during 6 seconds; the discussion was opened by M. A. Dollfus (Paris). C. Thomas and co-workers (Nancy) observed five cases of typhus and verified the vascular lesions already described in that disease; the discussion was opened by G. Bonamour (Lyons). F. Hervouet (Nantes) reported on the sections of several eyes with spontaneous retinal detachment; he felt that congenital anomalies might be responsible for this accident (choroidal lesions, anomalies of the pigmentary epithelium and of Bruch's membrane). The discussion was opened by L. Paufique (Lyons). M. Woillez and co-workers (Lille) observed two cases of temporal arteritis with abnormal symptoms (retinal nodules and optic neuritis); the discussion was opened by E. Bessière (Bordeaux). A. Baron and Le Bourhis-Gouray (Nantes) had studied, on patients and experimentally, the use of corticosteroids in cases of corneal herpes; the result varied according to the cases and to the age of the lesion. The discussion was opened by J. Legrand (Nantes).

All these papers and discussions will be published in a volume which usually comes out toward the end of the year and can be obtained by applying to Masson & Cie., 120 bd. Saint Germain, Paris 6.

During the meeting there were the usual operative sessions in the Paris hospitals and also a demonstration of patients treated by roentgentherapy for tumors at the Curie Institute. The *Ligue contre le Trachome* met on May 9 and on May 11, the International Association for the Prevention of Blindness. There were five meetings of the *Entretiens therapeutiques en Ophthalmologie*, which took place Thursday, May 14, through Saturday, May 16, and were devoted to the study of complications after eye surgery. The International Council of Ophthalmology met on the afternoon of Saturday, May 9.

The usual excursion took place on Wednesday afternoon, the members of the Society being taken to Compiègne by train and visiting the Château.

The usual banquet took place on Tuesday night and was particularly successful as it celebrated the 75 anniversary of the Society.

Books

Plastische Chirurgie am Auge. By E. von Walser. Pp. 258, with 285 illustrations. Price, not given. Springer-Verlag, Heidelberger Platz 3, Berlin, 1959.

This text, in German, covers the entire field of plastic surgery of the eye and its adnexa, and for those who read German fluently it is a well-illustrated reference text for this subject. An excellent bibliography is given.

Parsons' Diseases of the Eye. By Sir Stewart Duke-Elder. Thirteenth edition. Price, $8.75. Pp. 613, including index, with 459 illustrations, 22 in color. The Macmillan Company, 60 5th Ave., New York 11, 1959.

The first edition of this excellent textbook of ophthalmology appeared in 1907. It is gratifying to see that this 13th edition has been brought up to date and amplified by Sir Stewart in a manner which cannot be approached by any other English author. Sir John Parsons may not be known to many younger American ophthalmologists, but his multivolume text on ocular pathology was the authoritative English text on this subject and for many years after the editions were out of print was a prize collector's item. His monographs on color vision and form perception are still well worth reading if they can be obtained. They are long out of print.

In a certain sense this volume is a condensed Duke-Elder and can be used by the ophthalmologist preparing for Board examinations to great advantage. It is not suitable for medical students, since it is really a condensed textbook of ophthalmology for the postgraduate student.

Transplantation of Tissues (Skin, Cornea, Fat, Nerve, Teeth, Blood Vessels, Endocrine Glands, Organs, Peritoneum, Cancer Cells): Vol. II. Edited by Lyndon A. Pier, M.D. Price, $20. Pp. 690, including index. Williams & Wilkins Company, Mount Royal & Guilford Aves., Baltimore 2, 1959.

The first volume on the transplantation of tissues was published in 1955. This volume deals with the transplantation of specialized tissues, each chapter being contributed by a specialist in the field. The chapter on the cornea was done by Dr. Ramon Castroviejo. This chapter is disappointingly short, occupying only twenty-four pages, which makes it one of the shortest in the book.

The book begins with an excellent general résumé of cells and tissues and the zoologic laws of transplantation. The illustrations are excellent, owing largely to the use of a high-grade gloss paper.

Diseases of the Nose, Throat and Ear. Edited by Chevalier Jackson, M.D., and Chevalier L. Jackson, M.D. (with the collaboration of 61 outstanding authorities). Second Edition. Price, $20. Pp. 886, with 1193 illustrations, including 16 plates in color. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1959.

Sixty-one authorities have contributed to this well-known volume on diseases of the nose, throat, and ear. It will be used by ophthalmologists as an authoritative text whenever need is felt to seek information in this area of medicine.

The illustrations and printing are excellent.

Collected Reprints of the Francis I. Proctor Foundation for Research in Ophthalmology, University of California: Vol. II. 1954-1958.

Reprints of all manuscripts published from the Francis I. Proctor Foundation have been bound together and form a useful collection of research papers which might not be available to the average reader otherwise. Many of these papers have, of course, appeared in the two American journals of ophthalmology, but the others are reprints from less available sources. An index of authors and subjects

would be valuable, and it is hoped that in the future the Foundation will see fit to make this addition.

I. E. S. Lighting Handbook. Third Edition. Price, $10. Pp. 1100. Illuminating Engineering Society, 1860 Broadway, New York 23, 1959.

This is a standard book on lighting published by the Illuminating Engineering Society of America and provides the reader with essential information on light and lighting in simple terms and condensed style. This edition brings the subject up to date and includes chapters on the physics of light, light and vision, and the measurement of light and other radiant energy and chapters on the type of lighting needed for practically every type of industry and avocation in which light is used. For example, twenty-three pages are devoted to lighting in sports, and twenty pages to lighting in aviation. Miniature lamps are given consideration, as well as photographic lamps for taking pictures and for reproduction, projection, television, and radar.

This is an extremely comprehensive handbook and contains a great deal of useful information. It should be in every large library, to be used as a reference book.

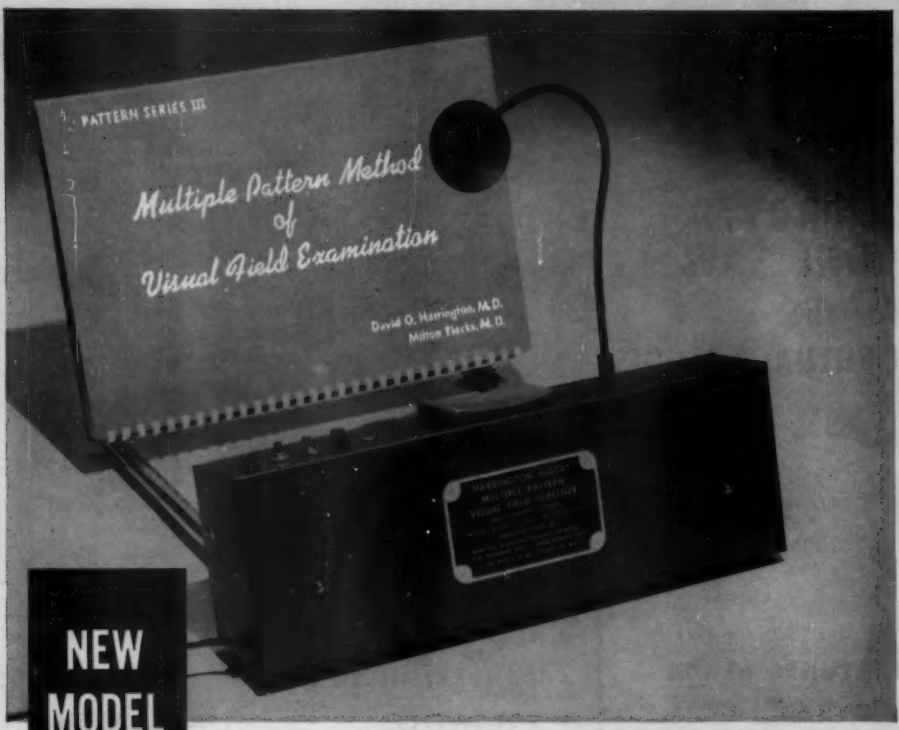
News and Comment

ANNOUNCEMENTS

Seminar on Glaucoma.—A seminar on glaucoma, with particular emphasis on gonioscopy and the study of the anterior angle, will be given at the Brooklyn Eye and Ear Hospital on Nov. 16, 17, and 18, 1959. Ample opportunity for practical instruction in the use of the gonioprism will be given and material from the glaucoma clinic will be utilized.

The course will be given by Doctor Daniel Kravitz, assisted by Drs. Mortimer A. Lasky, Nicholas P. Tantillo, and Samuel Zane. Registration is limited to six ophthalmologists only.

Application and the fee of $50 may be addressed to Dr. Daniel Kravitz, Brooklyn Eye and Ear Hospital, 29 Greene Ave., Brooklyn 38, N. Y.



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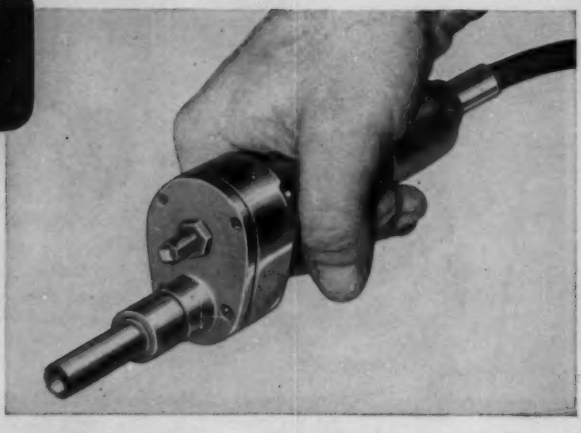

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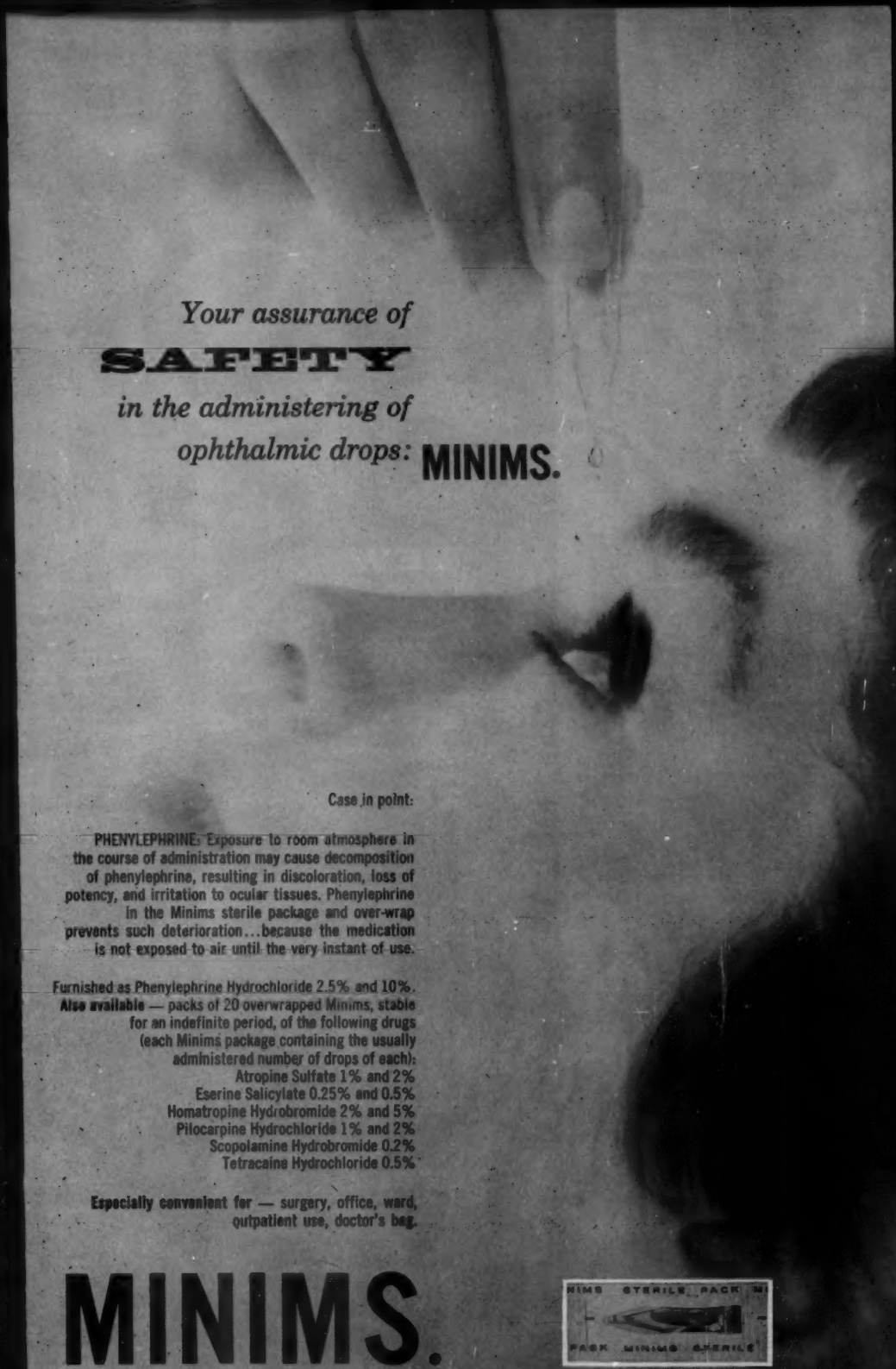

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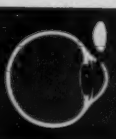
[1]Girard, Louis J., and Neely, Wanda: "The Evaluation of Zolyse in Cataract Extraction", Research Report No. 11, Alcon Laboratories, Inc., 1959.

[2]Boyd, Benjamin F.: Enzymatic Zonulysis, Highlights of Ophth., vol. III, no. 4, pg. 70, 1959.



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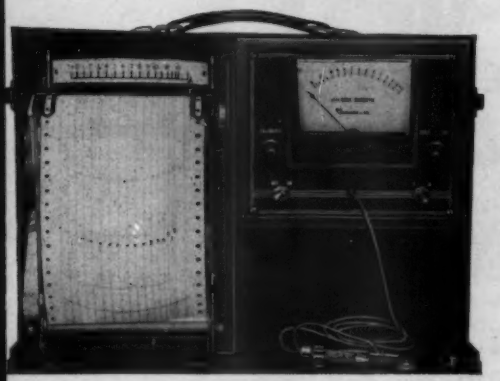

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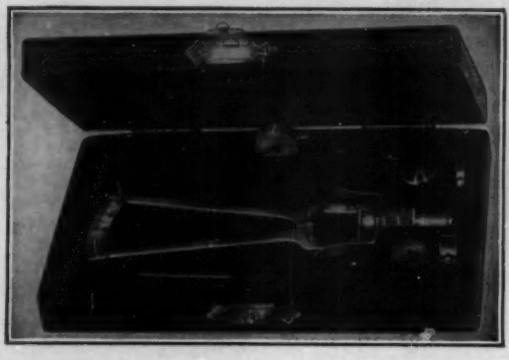

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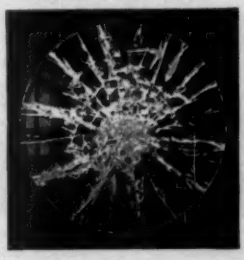

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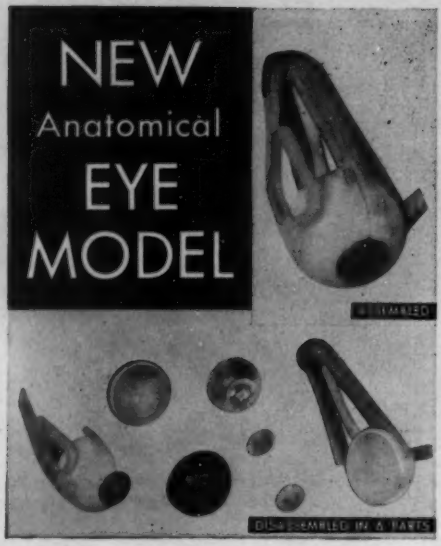

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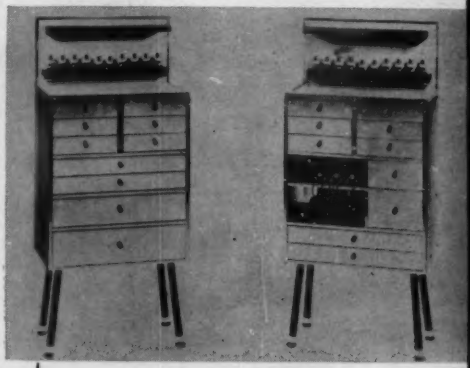

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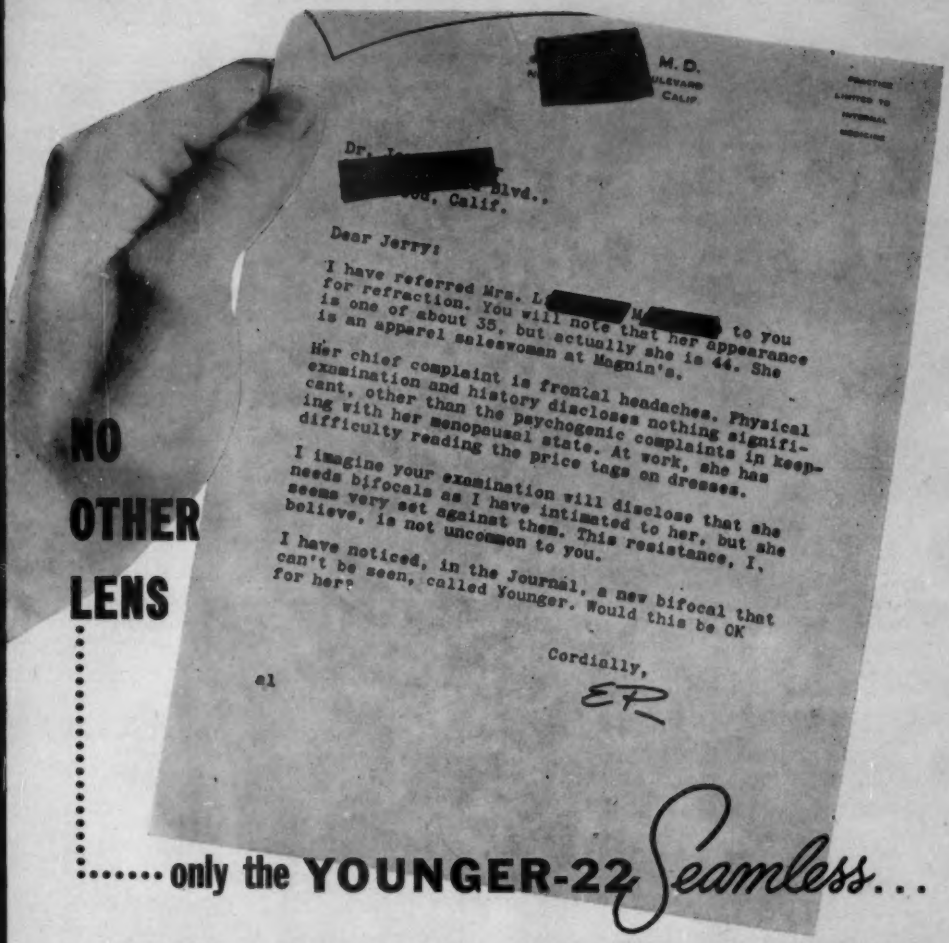
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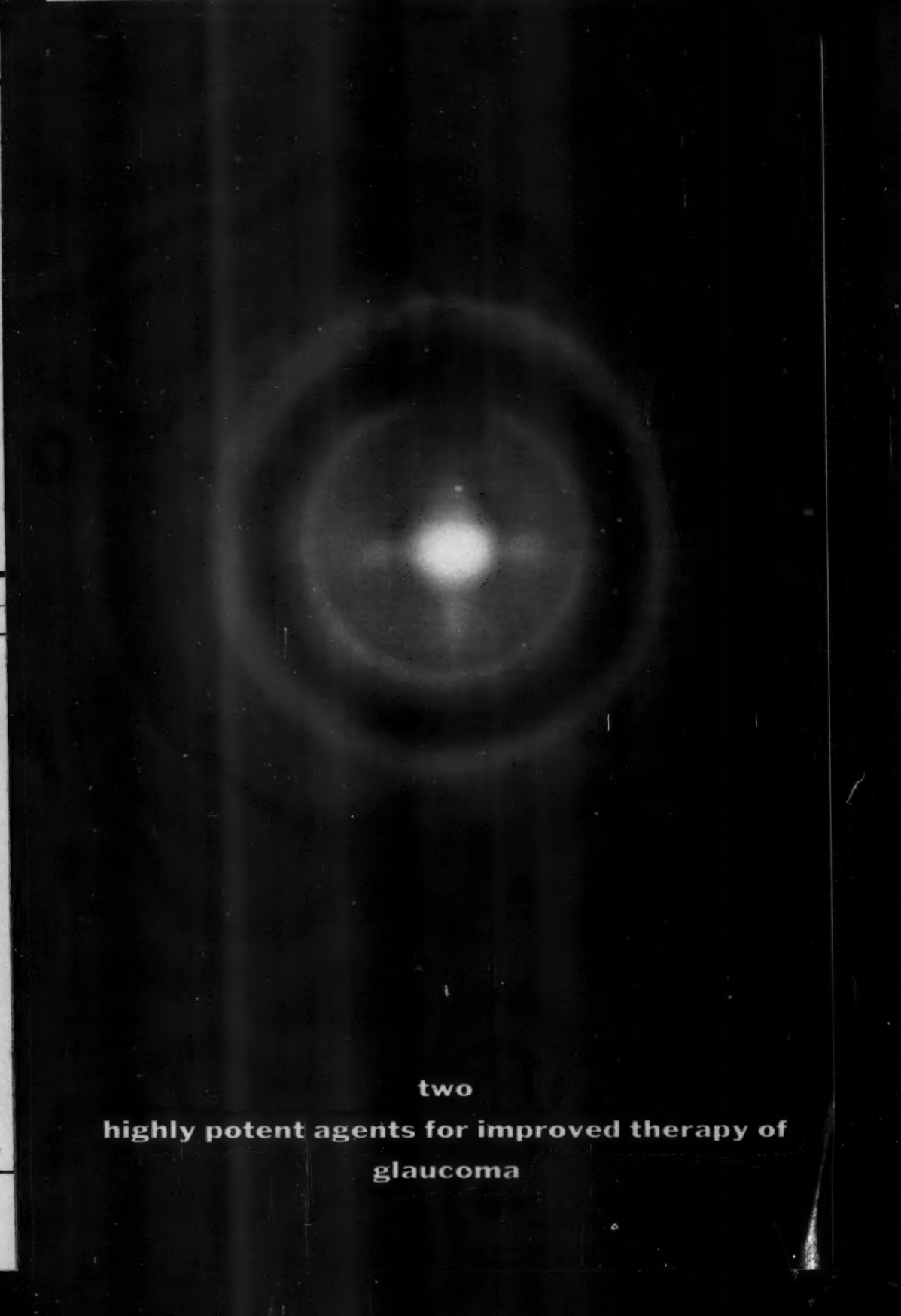
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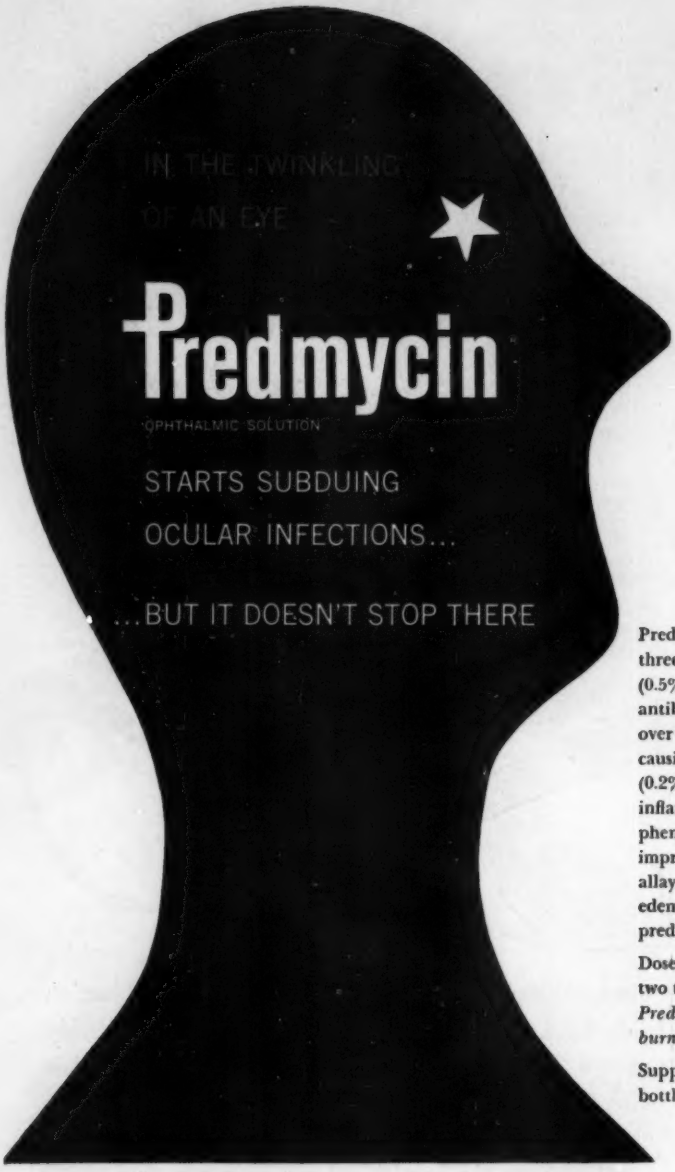

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